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Higher habitual flavonoid intakes are associated with a lower risk of peripheral artery disease hospitalizations

Nicola P Bondonno [1,2,3], Kevin Murray [4], Aedin Cassidy [3], Catherine P Bondonno [1,2], Joshua R Lewis [1,2], Kevin D Croft [2], Cecilie Kyrø [5], Gunnar Gislason [6,7,8], Christian Torp-Pedersen[9], Augustin Scalbert [10], Anne Tjønneland [5,11], Jonathan M Hodgson [1,2], Frederik Dalgaard [6].

[1] School of Medical and Health Sciences, Edith Cowan University, Perth, Australia (NPB; CPB; JRL; JMH);

[2] School of Biomedical Sciences, University of Western Australia, Royal Perth Hospital, Perth, Western Australia, Australia (NPB; CPB; JRL; KDC; JMH);

[3] Institute for Global Food Security, Queen's University Belfast, Northern Ireland (NPB; AC);

[4] School of Population and Global Health, University of Western Australia, Australia (KM);

[5] The Danish Cancer Society Research Centre, Copenhagen, Denmark (CK; AT);

[6] Department of Cardiology, Herlev & Gentofte University Hospital, Copenhagen, Denmark (GG; FD);

[7] The National Institute of Public Health, University of Southern Denmark, Odense, Denmark (GG);

[8] The Danish Heart Foundation, Copenhagen, Denmark (GG);

[9] Department of Clinical Investigation and Cardiology, Nordsjælland Hospital, Hillerød, Denmark (CT);

[10] International Agency for Research on Cancer, Lyon, France (AS);

[11] Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark (AT);

Conflicts of Interest

The authors declare no conflicts of interest.

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Corresponding author: Nicola P. Bondonno

School of Biomedical Sciences, Level 4, Medical Research Foundation

Rear 50 Murray St, Perth Western Australia, Australia WA 6000

Tel: +618 92240342

Email: n.bondonno@ecu.edu.au

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Abbreviations: confidence intervals (CI); chronic obstructive pulmonary disease (COPD); food frequency questionnaire (FFQ); hazard ratios (HRs); International Classification of Diseases (ICD); peripheral artery disease (PAD); polyunsaturated fatty acids (PUFAs); peripheral vascular disease (PVD).

Data described in the manuscript, code book, and analytic code will not be made available due to restrictions related to Danish law and the protection of patient privacy. The combined set of data as used in this study can only be made available through a trusted third party, Statistics Denmark. This state organisation holds the data used for this study.

ABSTRACT

Background: The role of nutrition in the primary prevention of peripheral artery disease (PAD), the third leading cause of atherosclerotic cardiovascular disease, is undetermined. Flavonoids may attenuate atherosclerosis and therefore persons who consume flavonoid-rich foods may have a lower risk of developing PAD.

Objective: To examine the association between flavonoid intake and PAD hospitalizations and investigate if the association differs according to established risk factors for PAD.

Design: Baseline data from 55,647 participants of the Danish Diet, Cancer and Health Study without PAD, recruited from 1993 to 1997, were cross-linked with Danish nationwide registries. Flavonoid intake was calculated from food frequency questionnaires using the Phenol-Explorer database. Associations were examined using multivariable-adjusted restricted cubic splines based on Cox proportional hazards models.

Results: After a median [IQR] follow-up time of 21 [20 – 22] years, 2,131 participants were hospitalized for any PAD. The association between total flavonoid intake and total PAD hospitalizations was non-linear, plateauing at approximately 750-1000 mg/day. Compared to the median flavonoid intake in quintile 1 (174 mg/d), an intake of 1000 mg/d was associated with a 32% lower risk of any PAD hospitalization [HR:0.68 (0.60, 0.77)], a 26% lower risk of atherosclerosis [HR:0.74 (0.62, 0.88)], a 28% lower risk of an aneurysm [HR:0.72 (0.59, 0.88)], and a 47% lower risk of a hospitalization for other peripheral vascular disease (PVD) [HR:0.53 (0.42, 0.67)]. A higher total flavonoid intake was also significantly associated with a lower incidence of revascularization or endovascular surgery and lower extremity amputation. The association between total flavonoid intake and PAD hospitalizations differed according to baseline smoking status, alcohol intake, BMI and diabetes status.

Conclusion: Ensuring the adequate consumption of flavonoid-rich foods, particularly in subpopulations prone to the development of atherosclerosis, may be a key strategy to lower the risk of PAD.

Keywords: nutrition; peripheral artery disease; primary prevention; cohort study; lifestyle

INTRODUCTION

Peripheral artery disease (PAD) is the atherosclerotic obstruction, or ischemia, of arteries and most commonly manifests in the lower extremities (1). PAD prevalence rises steeply with age; in high income countries, such as Denmark, PAD prevalence is <7% for persons in their 50's, >10% for persons in their 60's and >18% for persons in their 80's (2). In 2010, over 200 million adults worldwide had PAD (2). With the aging of the global population, it is likely that PAD will become increasingly common (2). PAD is associated with cardiovascular disease morbidity and mortality (3) and the most common symptom of PAD, intermittent claudication, can induce considerable suffering and limit walking ability (4). Furthermore, severe PAD can lead to limb ischemia and amputations of the lower extremities. The public health significance of PAD calls for evidence-based primary prevention strategies.

The role that nutrition plays in the primary prevention of PAD is currently uncharacterized. Flavonoids, polyphenolic compounds found ubiquitously in plant-derived foods and beverages such as fruits, vegetables, dark chocolate, tea, and red wine (5), have been shown to improve nitric oxide bioavailability and endothelial function and decrease blood pressure and inflammation (6). The main risk factors for PAD are age, smoking and diabetes mellitus. They are thought to contribute to PAD development by an increase in inflammation, increase in arterial stiffness, decrease in nitric oxide, increase in oxidative stress, and a decrease in vasodilation (7); Thus, flavonoid-rich foods could be important moderators of PAD. While there is some evidence that higher flavonoid intakes are associated with a lower incidence of PAD (8), larger, longer-term epidemiological studies are needed to further examine potential associations.

We have previously shown that higher total flavonoid intakes are associated with lower atherosclerotic cardiovascular disease hospitalizations, and, more specifically, lower PAD

hospitalizations (9). However, unexplored areas include: whether the prevalence of risk factors modifies the association between flavonoids and incidence of PAD hospitalization; associations of individual flavonoid subclasses and individual flavonoid compounds with PAD; associations of flavonoids with subtypes of PAD such as atherosclerosis, aneurysm, embolism or thrombosis, and other peripheral vascular diseases; and associations of flavonoids with PAD-related procedures such as revascularizations or endovascular surgery, and amputations.

Therefore, the primary aim of this study was to investigate the association of total flavonoid and flavonoid subclass intakes with PAD hospitalizations in the Danish Diet, Cancer, and Health cohort. Secondary aims were to investigate whether these associations differed according to the presence of risk factors for PAD.

METHODS:

Study Population

Participants were recruited from of the greater areas of Copenhagen and Aarhus, between 1993 and 1997, as part of the Danish Diet, Cancer, and Health study. Of the 57 053 participants recruited, 56 468 completed a food frequency questionnaire (FFQ) and were without a cancer diagnosis prior to enrolment. All Danish residents are assigned a unique and permanent number allowing cross-linking of participants to nationwide registers. The following databases were cross-linked to the cohort: The Civil Registration System, The Integrated Database for Labor Market Research Database, and The Danish National Patient Register, which contains information on all hospital admissions in Denmark since 1978. This includes one primary diagnosis and one or more secondary diagnoses defined by the

International Classification of Diseases (ICD): the 8th revision (ICD-8) until 1993 and the 10th revision (ICD-10) from 1994 (10). Participants were excluded if they had improbable energy intakes [<2,092 kJ/day (<500 kcal/day) and >20,920 kJ/day (>5,000 kcal/day)] (n=202) or if they had missing covariates or were extreme outliers (n=218). Finally, participants were excluded if they had any prevalent PAD (n=401): a prior diagnosis of atherosclerosis (ICD-8: 440, 414, ICD-10: I70), aortic aneurysm (ICD-8: 441, ICD-10: I71), other aneurysm (ICD-8: 442, ICD-10: I72), other peripheral vascular disease (PVD) (ICD-8: 443, ICD-10: I73), or arterial embolism and thrombosis (ICD-8: 444, ICD-10: I74) (**Supplementary Figure 1**)

This study was approved by the Danish Data Protection Agency (Ref no 2012-58-0004 I-Suite nr: 6357, VD-2018-117).

Exposures

Exposures were intakes of total flavonoids, flavonoid subclasses, and individual flavonoid compounds with mean intakes >5mg/day. Calculations of flavonoid intake have been described previously (11). Briefly, estimates of the flavonoid content of all foods and beverages in the FFQ were obtained from the Phenol-Explorer database (12). As the average intakes of isoflavones, dihydrochalcones, dihydroflavonols, and chalcones were <5mg/day, they were not included in the individual subclass analyses. Total flavonoid intake was calculated by summing each of the 219 flavonoid aglycones.

Study outcomes

The primary outcome was first-time PAD hospitalization. PAD was defined as hospitalization with a primary or secondary diagnosis code for atherosclerosis, aneurysm (aortic and other), arterial embolism or thrombosis, or other PVD (ICD-8 or ICD-10 as described above). Other PVD diagnoses were primarily unspecified PVD, more specifically, intermittent claudication.

Secondary outcomes were atherosclerosis, aneurysm (aortic and other), arterial embolism or thrombosis, or other peripheral vascular disease, discretely. These ICD codes for PAD hospitalization have a positive predictive value of 81.2% in the Danish National Patient Register (13).

PAD-related procedures

To assess the association between flavonoid intake and PAD-related procedures, we obtained the following procedure codes from the Danish National Patient Register: major amputation of the lower extremities (above ankle), and vascular reconstruction and endovascular procedures of the central or lower extremity peripheral arteries (**Supplementary Table 1**). As the The Danish National Patient Register only started recording procedure codes in 1996, data was left truncated to 1st January, 1996. As such, for this outcome analysis, 66 participants were excluded as they died and 9 participants were excluded as they developed PAD, before 1st January, 1996 (n=55 572).

Validated case analysis

To verify the registry-based outcomes, we re-examined associations using only medically reviewed and validated cases (ICD-10: I702, I702A, I739A, I739B, I739C), with follow-up between August, 1994 and December, 2009. Validation was undertaken by scrutinizing all medical records using pre-specified criteria for a diagnosis of PAD, described in more detail previously (13). Due to prior diagnosis of validated PAD, a further 7 participants were excluded in this analysis (n=55,640).

Covariates

Data on sex, age, education, smoking habits, alcohol consumption, daily activity, and diet were obtained from questionnaires completed by participants upon study enrolment. Smoking status was defined as "current smoker" if the participant indicated that they currently smoke daily, "previous smoker" if the participant indicated that they smoked daily for at least one year at any stage of their life, and "never smoker" if the participant was neither a current nor a previous smoker, as defined above. Anthropometry and total cholesterol were measured at the study centers. Average annual income over 5-years (defined as household income after taxation and interest, using the value of the Danish currency in 2015) was used to represent socio-economic status. ICD-8 and ICD-10 codes were used to determine prevalent chronic kidney disease, chronic obstructive pulmonary disease (COPD), ischemic heart disease, ischemic stroke, heart failure, atrial fibrillation, and cancers (**Supplementary Table 2**). For hypertension and diabetes mellitus, self-reported data were used due to underreporting of these diagnosis in the Danish National Patient Register (14).

Statistical Analysis

Participants were followed from the date of enrolment until the date of PAD hospitalization, death, emigration, or end of follow-up (August, 2017), whichever came first. Nelson-Aalen plots of cumulative incidence for PAD with a competing risk of death, as well as by quintiles of total flavonoid intake, were computed. Quintiles were derived separately for each exposure variable. Multivariable Cox proportional hazards models were used to investigate relationships between the exposures of interest and all outcomes, fitting a separate model for each exposure of interest and outcome combination. To allow the association between the exposure and outcome to be non-linear, the modelling of continuous exposure variables was carried out using restricted cubic splines using the 'rms' R package with the rcs() function (see (15) for a practical description of this). For presentation purposes (but not for modelling)

quintiles of the exposure variable were generated and the median value of each quintile calculated. Hazard ratios (HRs) calculated from each of the fitted models described above, relative to a reference value of the median of the first quintile of the relevant exposure variable, were plotted against the exposure variable, with 95% confidence bands provided. Using these values, HRs were calculated from the fitted models comparing the median of each quintile to the reference value of the median in quintile 1, and tabulated with 95% confidence intervals. Individuals with intakes more than 4 standard deviations above the mean were excluded from the spline analysis. Four models of adjustment were used: 1) minimally adjusted: age and sex; 1b) multivariable-adjusted: age, sex, BMI, smoking status (current/former/never), physical activity (total daily metabolic equivalent), pure alcohol intake (g/d), and socio-economic status (income); 2) multivariable-adjusted including total energy intake and potential dietary confounders: all variables in Model 1b plus energy intake (kJ/day) and intakes (g/d) of fish, red meat, processed meat, polyunsaturated fatty acids, monounsaturated fatty acids and saturated fatty acids; 3) multivariable-adjusted including covariates that may be on the causal pathway: all variables in Model 1b plus hypertension (yes/no), hypercholesterolemia (yes/no), and prevalent disease (stroke, ischemic heart disease, heart failure, diabetes, chronic obstructive pulmonary disease, chronic kidney disease, and cancer; entered into the model separately). Covariates were chosen *a priori* to the best of our knowledge of potential confounders of flavonoid intake and PAD. Cox proportional hazards assumptions were tested using log-log plots of the survival function versus time and assessed for parallel appearance. All deaths were censored rather than treated as a competing risk (16). As the presence of major chronic diseases may influence the diet, as it was captured at baseline, and result in a bias, we conducted a sensitivity analysis where all participants with a comorbidity at baseline were excluded. In addition, due to no censoring in this cohort, standard logistic regression models were used to obtain the 20-year absolute risk

estimates of PAD. For these analyses, a binary outcome indicating the presence PAD hospitalization during 20 years of follow-up was used. Unless indicated by the stratification variable, these estimates are for a non-smoking participant, aged 56 years, with a BMI of 25.5 kg/m2, a total daily metabolic equivalent score of 56, with a mean household income of 394 701 – 570 930 DKK/year, and an alcohol intake of 13 g/day. Emerging evidence suggests that flavonoids may afford greater protection to those with lifestyle habits placing them at a higher risk of CVD (9); to investigate the associations differ according to established risk factors for PAD, firstly, p-values for interaction terms were obtained from likelihood ratio tests of Cox proportional hazards models with and without the interaction term and, secondly, all analyses were stratified by risk factors for PAD (17) for which data had been collected at baseline (smoking status, alcohol intake, BMI, sex, diabetes status, cholesterol levels, and hypertension status). As there is potential for residual confounding, when stratifying by smoking status (never smoker or ever smoker (current for previous smoker)), alcohol intake, and BMI, the corresponding continuous variables (smoking pack-years, alcohol intake and BMI, respectively) were included in the model where appropriate. We chose stratification cut-off points of 20 g pure alcohol per day, and a BMI of 30 kg/m^2 as done previously in this cohort (11). All analyses were undertaken using STATA/IC 14.2 (StataCorp LLC) and R statistics (R Core Team, 2019 (18)). Statistical significance was set at $p \leq 0.05$ (two-tailed) for all tests.

RESULTS

This population of 55,647 Danish residents, with a median [IQR] age of 56 [52-60] years at entry, had a median [IQR] follow-up of 21 [20 – 22] years. During a maximum of 23 years of follow-up, 2,131 individuals were hospitalized for any form of PAD. For PAD subtypes, 993 were hospitalized for atherosclerosis, 800 for an aneurysm, 161 for an embolism or

thrombosis, and 653 for other PVD. Some participants received more than one PAD diagnosis. During follow-up, 799 participants underwent revascularization or endovascular surgery and 242 had a lower extremity amputation. Furthermore, 12,738 participants died from any cause without a PAD hospitalization. The cumulative incidence of PAD hospitalizations and death without a PAD hospitalization is shown in **Supplementary Figure 2.**

Baseline characteristics

Compared to participants with the lowest flavonoid intakes, those with the highest habitual intakes were more likely to be female, have a lower BMI, be more physically active, have a higher degree of education, have a higher income, and were less likely to have ever smoked or to be hypercholesteraemic. Furthermore, they tended to eat more fish, dietary fibre, fruits, and vegetables, and eat less red and processed meat (**Table 1**).

Associations between total flavonoid intake and PAD-related hospitalizations and procedures

The association between total flavonoid intake and total PAD hospitalizations was non-linear; restricted cubic splines show a threshold of the inverse association at approximately 750-1000 mg/day (**Figure 1**). Compared to a total flavonoid intake of 174 mg/d (median intake in quintile 1) and after multivariable adjustments (Model 1b), an intake of 1000 mg/d was associated with a 32% lower risk of a hospitalization for PAD [HR (95% CI)] [0.68 (0.60, 0.77)]. Associations between total flavonoid intake and PAD hospitalization subtypes are shown in Figure 1 and **Supplementary Table 3**. A total flavonoid intake of 1000 mg/d was associated with a 26% lower risk of a hospitalization for atherosclerosis [0.74 (0.62, 0.88)], a 28% lower risk of a hospitalization for an aneurysm [0.72 (0.59, 0.88)], a non-significant 27% lower risk of a hospitalization for an arterial embolism or thrombosis [0.73 (0.46, 1.13)],

and a 47% lower risk of a hospitalization for other PVD [0.53 (0.42, 0.67)]. The association between total flavonoid intake and PAD-related procedures appeared to be "u-shaped" (**Figure 2**). Compared to a total flavonoid intake of 174 mg/d, the lowest risks were seen for intakes of 1000 mg/d for revascularizations/endovascular surgery [HR: 0.57 (95% CI 0.46, 0.69)], and 500 mg/d for amputations [HR: 0.56 (95% CI 0.43, 0.74)], after multivariable adjustments (Model 1b). Associations were subtly strengthened, in that HR's became more extreme, in a sensitivity analysis excluding all participants with a comorbidity at baseline (n=4 779 excluded; n=50 868 remaining in the analysis; data not shown).

Associations between flavonoid subclass intakes and PAD-related hospitalizations

For all flavonoid subclasses, after multivariable adjustments, participants in quintiles 2-5 had a lower risk of a PAD hospitalization compared to participants in quintile 1 (**Table 2**). HRs after adjustments for covariates that are both confounders and on the causal pathway (Model 3) are presented in **Supplementary Table 4** but do not differ substantively. Associations were strongest for the flavonol and flavanol oligo+polymers subclasses where participants in quintile 5 had a 32% [Q5 vs Q1 HR: 0.68 (0.60, 0.77)] and 33% [Q5 vs Q1 HR: 0.67 (0.59, 0.77)] lower risk of a PAD hospitalization, respectively, after multivariable adjustments (Model 1b; Table 2). All subclasses were non-linearly associated with PAD hospitalizations, with thresholds occurring at varying levels of intake (**Figure 3**).

Associations between major flavonoid compound intakes and PAD-related hospitalizations

Associations between all individual flavonoid compounds with mean intakes >5mg/day and PAD hospitalizations are presented in **Table 3** and **Figure 4**. For the flavanol monomer subclass, we present only the results for epicatechin as the flavanol monomers are derived primarily from the same food sources, and thus have a very high correlation (Pearson's

correlations ranged from 0.89 – 1.00) and very similar HRs. Intakes above those in quintile 1 for all individual flavonoid compounds were associated with a lower risk of a PAD hospitalization after multivariable adjustments.

Associations between total flavonoid intakes and PAD hospitalizations stratified by risk factors for PAD

On a relative scale, the association between total flavonoid intake and PAD hospitalizations appeared to differ according to baseline smoking status, BMI, and diabetes status; higher total flavonoid intakes were only associated with a significantly lower risk of PAD hospitalizations in smokers, normal to overweight participants, and those without diabetes at baseline (**Figure 5**). However, on an absolute scale, the 20-year absolute risk difference between an average male or female participant in Q5 versus Q1 was greatest for current smokers (male: 2.61%; female: 1.55%) and those with diabetes at baseline (male: 2.11%; female: 1.27%); there was no difference based on alcohol intake or BMI (**Supplementary Tables 5 and 6**). The association did not differ according to sex, cholesterol levels, or hypertension status on an absolute or a relative scale (Figure 5 and Supplementary Tables 5 and 6). The sample size and number of events for each subgroup are presented in **Supplementary Table7**.

Validated case analysis

Using only validated cases, 950 participants were hospitalized for PAD. Compared to a total flavonoid intake of 174 mg/d and after multivariable adjustments (Model 1b), an intake of 1000 mg/d was associated with a 38% lower risk of a PAD hospitalization [HR: 0.62 (0.51, 0.74); **Supplementary Figure 3**].

DISCUSSION

A primary prevention approach incorporating nutrition strategies may be advantageous in reducing the global burden and considerable associated morbidity of PAD. In this prospective cohort study, conducted in 55 647 Danish residents free of PAD at baseline, higher intakes of total flavonoids, and all flavonoid subclasses, were non-linearly associated with a lower risk of PAD hospitalizations. Furthermore, higher total flavonoid intakes were associated with lower risks of hospitalizations for atherosclerosis, aneurysms, and other PVD (primarily intermittent claudication), and both revascularization or endovascular surgery and lower extremity amputations. On both a relative and an absolute scale, the greatest benefits observed for higher flavonoid intakes were in current or former smokers.

The role that nutrition plays in the primary prevention of PAD is not well understood. Previous observational studies suggest that a diet characterized by a low intake of vitamins, dietary fibre, and poly-unsaturated fatty acids (PUFAs), and a high intake of red meat, is associated with a higher incidence of PAD (19-21). Due to the underlying pathogenesis of PAD, a recent review summarizing current knowledge on nutritional patterns among patients with PAD strongly advocates for a diet rich in foods with anti-inflammatory and antioxidant properties (22). One such diet, the Mediterranean-style diet, is characterized by a high intake of extra virgin olive oil, vegetables, fruits, nuts and pulses and legumes, and a moderate intake of red wine, all of which are rich sources of flavonoids (23). Evidence for the beneficial effects of the Mediterranean style diet in the primary prevention of PAD comes from a post hoc analysis of the PREDI-MED trial (24). However, there is a lack of information on the potential benefits of a flavonoid-rich diet in mitigating PAD. We have demonstrated that flavonoid intake is inversely associated with atherosclerotic cardiovascular disease, most strongly for PAD (9). In a previous case-control study (n=200), a higher

flavonoid intake was associated with a lower odds of peripheral arterial occlusive disease, where the odds ratios (95% CI) for a one standard deviation higher total flavonoid intake was 0.46 (0.28, 0.77) (8). Furthermore, the strongest associations were observed for the flavonol, flavone, and flavan-3-ols subclasses. In the present study, inverse associations appeared to be the strongest for the flavonol and flavanol oligo+polymers subclasses. It is likely that tea, chocolate, wine, apples, and pears were the main food sources of these subclasses in the present cohort (25). Although caution must be taken when interpreting these findings as they are on a relative scale, both true biological variability and greater precision in the estimation of intakes of these flavonoid subclasses may explain these stronger associations. The inverse associations observed between flavonoid intake and both revascularization or endovascular surgery and major amputation procedures, suggests that flavonoids may play a role not only in the development of PAD, but also in the progression of PAD.

The main risk factors for PAD, age, smoking, and diabetes mellitus, can cause an increase in inflammation, arterial stiffness, and oxidative stress, and a decrease in nitric oxide bioavailability with a concomitant decrease in vasodilation (7). Flavonoids may impede the initiation and progression of PAD by restoring endothelial homeostasis through the augmentation of nitric oxide bioavailability and by attenuating inflammation through upregulation of the anti-inflammatory Nrf2 pathway and downregulation of the pro-inflammatory NF-κβ pathway (6). The present study found that in current and former smokers, a higher flavonoid intake was strongly associated with a lower risk of PAD, supporting the hypothesis that flavonoids may play a role in counteracting inflammation and oxidative stress in these participants. Setting a precedence for this finding, an inverse association between fruit and vegetable intake and PAD incidence was shown to only be present in current or former smokers (26). It may be that flavonoids only exhibit detectable PAD-preventing effects in settings of significant inflammation and oxidative stress, such as

that induced by smoking. That no significant association was observed in non-smokers, and statistical tests for interaction were not significant, may be due to the very low number of events in this subgroup. Importantly, although these findings suggest that flavonoids may afford more protection against PAD to smokers, smokers with a high flavonoid intake were still at a higher risk of PAD than non-smokers with a low flavonoid intake. Although, the hazard ratio of PAD was lower for high alcohol consumers than low alcohol consumers with a total flavonoid intake above 500 mg per day, the absolute risk difference between high and low flavonoid intake for these two groups was comparable. Similarly, although there was evidence that the associations differed according to baseline BMI on a relative scale, the absolute risk difference between high and low flavonoid intake was the same for those who were normal or overweight and those who were obese. Conversely, although on a relative scale there was evidence that flavonoid intake was not associated with PAD in persons with diabetes, on an absolute scale, the absolute risk difference between high and low flavonoid intake for an average male participant with diabetes was notable (2.11%). These results should be interpreted with caution and warrant further investigation as few participants had prevalent diabetes at baseline (n=1 152). These findings suggest that the mechanisms by which flavonoids ameliorate atherosclerosis may interact with the mechanisms by which smoking and diabetes lead to atherosclerosis.

Our results emphasize the importance of a flavonoid-rich diet in mitigating PAD risk. Despite the positive findings of the present study, evidence from randomized controlled trials is urgently needed. Future interventional studies of flavonoid intake should include patients at risk for PAD and investigate early markers of PAD such as the ankle-brachial-index.

Limitations

Due to the observational nature of the study we are not able to infer causality or rule out residual confounding. We acknowledge common food frequency questionnaire limitations, in particular that not all flavonoid-rich foods, for example berries, were included in the questionnaire. We acknowledge that flavonoid intake may have changed over the 23 years of follow up; however this would have likely attenuated any associations. Furthermore, the associations observed cannot be attributed to flavonoid intake alone, as participants with higher flavonoid intakes tended to have a healthier underlying dietary pattern, eating more fruits and vegetables and less red and processed meat. However, flavonoid intake was strongly associated with PAD after adjustments were made for a number of potential dietary confounders. We were unable to determine the association between flavonoid intake and outpatient visits for PAD, due to low validity of outpatient diagnoses. Misclassification bias is always present when using registry-based outcomes; however, our validated cases analysis gave similar results meaning that bias was limited. The lack of clinical measurements specific for PAD such as ankle-brachial index could have provided additional valuable information on PAD severity and flavonoid intake.

Conclusion

A diet rich in flavonoids was strongly associated with a lower risk of a hospitalization for PAD, revascularizations or endovascular surgery, and lower extremity amputations. Therefore, ensuring an adequate intake of flavonoid-rich foods may be helpful in mitigating PAD risk.

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None.

355 **Authors' Contributions:**

356 NPB, FD, KM, AC, and JMH designed research (project conception, development of overall
357 research plan, and study oversight); AT conducted the original cohort study; AS and CK
358 calculated flavonoid intake from FFQ data; NPB, KM and FD analyzed data; NPB and FD
359 wrote the paper and had primary responsibility for final content; KM, AC, CPB, JRL, KDC,
360 CK, GG, CTP, AS, AT, and JMH assisted with interpretation of the results and critically
361 reviewed the manuscript. All authors read and approved the final version of the manuscript.

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Table 1. Baseline characteristics of study population

	Total population n = 55647	**Total flavonoid intake quintiles**				
		Q1 n = 11130	**Q2 n = 11129**	**Q3 n = 11130**	**Q4 n = 11129**	**Q5 n = 11129**
Total flavonoid intake (mg/d)	496 [287–805]	174 [128–213]	321 [287–357]	496 [443–549]	727 [660–805]	1 202 [1025–1436]
Sex (male)	26429 (47.5)	6417 (57.7)	5693 (51.2)	5290 (47.5)	4948 (44.5)	4081 (36.7)
Age (years)	56 [52–60]	56 [52–60]	56 [52–60]	56 [52–60]	56 [52–60]	55 [52–59]
BMI (kg/m^2)	25.5 [23.3–28.2]	26.1 [23.8–28.9]	25.9 [23.6–28.5]	25.6 [23.3–28.3]	25.3 [23.2–27.9]	24.9 [22.7–27.4]
MET score	56.5 [37.0–84.8]	51.0 [32.0–78.0]	55.5 [36.3–84.0]	57.3 [38.0–85.0]	58.3 [38.5–87.0]	60.0 [39.8–88.5]
Smoking status						
Never	19628 (35.3)	2741 (24.6)	3740 (33.6)	3983 (35.8)	4444 (39.9)	4720 (42.4)
Former	16027 (28.8)	2673 (24.0)	3017 (27.1)	3243 (29.1)	3563 (32.0)	3531 (31.7)
Current	19992 (35.9)	5716 (51.4)	4372 (39.3)	3903 (35.1)	3122 (28.1)	2879 (25.9)
Education						
≤7 years	18248 (32.8)	5066 (45.5)	4222 (37.9)	3555 (31.9)	3006 (27.0)	2399 (21.6)
8–10 years	25677 (46.1)	4876 (43.8)	5234 (47.0)	5326 (47.9)	5266 (47.3)	4975 (44.7)
≥11 years	11694 (21.0)	1182 (10.6)	1669 (15.0)	2244 (20.2)	2850 (25.6)	3749 (33.7)
Mean household income						
≤394,700 DKK/year	13753 (24.7)	3293 (29.6)	2713 (24.4)	2685 (24.1)	2560 (23.0)	2502 (22.5)
394,701–570,930 DKK/year	13914 (25.0)	3241 (29.1)	2993 (26.9)	2693 (24.2)	2582 (23.2)	2405 (21.6)

570,931–758,297 DKK/year	13965 (25.1)	2918 (26.2)	3004 (27.0)	2879 (25.9)	2604 (23.4)	2560 (23.0)
> 758,297 DKK/year	14015 (25.2)	1678 (15.1)	2419 (21.7)	2872 (25.8)	3383 (30.4)	3663 (32.9)
Hypertensive	9006 (16.2)	1779 (16.0)	1832 (16.5)	1833 (16.5)	1808 (16.2)	1754 (15.8)
Hypercholesterolemic	4088 (7.3)	877 (7.9)	808 (7.3)	833 (7.5)	848 (7.6)	722 (6.5)
Comorbidities						
Diabetes	1152 (2.1)	266 (2.4)	216 (1.9)	246 (2.2)	215 (1.9)	209 (1.9)
Heart failure	200 (0.4)	48 (0.4)	50 (0.4)	36 (0.3)	37 (0.3)	29 (0.3)
Atrial fibrillation	274 (0.5)	55 (0.5)	55 (0.5)	59 (0.5)	49 (0.4)	56 (0.5)
Ischemic heart disease	2101 (3.8)	546 (4.9)	404 (3.6)	424 (3.8)	383 (3.4)	344 (3.1)
Ischemic stroke	734 (1.3)	206 (1.9)	140 (1.3)	135 (1.2)	125 (1.1)	128 (1.2)
COPD	844 (1.5)	219 (2.0)	185 (1.7)	155 (1.4)	156 (1.4)	129 (1.2)
CKD	199 (0.4)	42 (0.4)	32 (0.3)	44 (0.4)	41 (0.4)	40 (0.4)
Cancer	241 (0.4)	52 (0.5)	42 (0.4)	58 (0.5)	33 (0.3)	56 (0.5)
Medication use						
Insulin treated	374 (0.7)	76 (0.7)	64 (0.6)	82 (0.7)	81 (0.7)	71 (0.6)
Antihypertensive	6794 (12.2)	1339 (12.0)	1403 (12.6)	1381 (12.4)	1350 (12.1)	1321 (11.9)
Statin	1 021 (1.8)	240 (2.2)	205 (1.8)	208 (1.9)	206 (1.9)	162 (1.5)
HRT						
Never	15885 (28.5)	2594 (23.3)	3031 (27.2)	3258 (29.3)	3248 (29.2)	3754 (33.7)
Current	8780 (15.8)	1291 (11.6)	1559 (14.0)	1687 (15.2)	1999 (18.0)	2244 (20.2)
Former	4521 (8.1)	819 (7.4)	842 (7.6)	887 (8.0)	928 (8.3)	1045 (9.4)
NSAID	17998 (32.6)	3482 (31.5)	3496 (31.6)	3626 (32.8)	3606 (32.6)	3788 (34.3)
Aspirin	7009 (12.6)	1362 (12.2)	1343 (12.1)	1430 (12.8)	1382 (12.4)	1492 (13.4)
Dietary characteristics						

Energy (kcal)	2271 [1878–2717]	2060 [1681–2485]	2213 [1844–2629]	2330 [1944–2768]	2375 [1988–2828]	2373 [1975–2842]
Total fish intake (g/d)	38 [25–55]	33 [22–49]	38 [25–54]	39 [27–57]	41 [28–59]	40 [27–57]
Red meat intake (g/d)	78 [57–107]	80 [58–108]	81 [59–110]	80 [58–110]	78 [57–107]	72 [52–99]
Processed meat intake (g/d)	25 [14–40]	28 [17–45]	26 [15–42]	25 [14–40]	23 [14–38]	20 [11–34]
Dietary fibre intake (g/d)	20 [16–25]	17 [13–20]	19 [16–23]	21 [17–25]	22 [18–27]	23 [19–29]
Total carbohydrate intake (g/d)	246 [201-297]	213 [174-256]	239 [199-285]	253 [208-303]	264 [217-316]	267 [218-323]
Saturated FA (g/d)	31 [24–39]	29 [23–37]	31 [24–39]	32 [24–40]	32 [25–41]	32 [24–41]
Polyunsaturated FA (g/d)	13 [10–17]	12 [9–16]	13 [10–17]	14 [10–18]	14 [11–18]	14 [10–18]
Monounsaturated FA (g/d)	27 [21–35]	26 [20–34]	27 [21–35]	28 [22–35]	28 [22–35]	27 [21–34]
Fruit intake (g/d)	172 [95–282]	88 [45–142]	162 [98–239]	193 [114–301]	225 [140–360]	240 [141–390]
Vegetable intake (g/d)	162 [105–231]	115 [72–171]	150 [100–212]	168 [114–236]	185 [127–254]	196 [136–272]
Alcohol intake (g/d)	13 [6–31]	11 [3–24]	13 [6–25]	15 [6–34]	14 [7–32]	13 [6–32]

Data expressed as median [IQR] or n (%), unless otherwise stated.

BMI, body mass index; CKD, chronic kidney disease; COPD, common obstructive pulmonary disease; DKK, Danish Krone; FA, fatty acids; HRT, hormone replacement therapy, MET, metabolic equivalent; NSAID, Nonsteroidal anti-inflammatory drug.

Table 2. Hazard ratios of peripheral arterial disease hospitalizations by quintiles of flavonoid intake

	Flavonoid intake quintiles				
	Q1 (n=11130)	**Q2 (n=11129)**	**Q3 (n=11130)**	**Q4 (n=11129)**	**Q5 (n=11129)**
Total Flavonoids					
No. events	648	471	404	324	284
Intake (mg/d)[1]	174 (6–251)	321 (251–395)	496 (395–602)	727 (602–909)	1202 (909–3552)
HR (95% CI)					
Model 1	ref.	0.71 (0.65, 0.76)	0.55 (0.50, 0.61)	0.49 (0.44, 0.55)	0.47 (0.42, 0.53)
Model 1b	ref.	0.83 (0.77, 0.89)	0.73 (0.66, 0.80)	0.69 (0.61, 0.77)	0.69 (0.61, 0.78)
Model 2	ref.	0.85 (0.79, 0.92)	0.77 (0.70, 0.85)	0.74 (0.65, 0.83)	0.75 (0.66, 0.86)
Flavonols					
No. events	699	443	385	321	283
Intake (mg/d)[1]	15 (0–21)	26 (21–32)	39 (32–50)	66 (50–83)	116 (83–251)
HR (95% CI)					
Model 1	ref.	0.70 (0.66, 0.75)	0.54 (0.49, 0.60)	0.46 (0.41, 0.51)	0.46 (0.40, 0.51)
Model 1b	ref.	0.81 (0.76, 0.87)	0.70 (0.63, 0.77)	0.65 (0.58, 0.73)	0.68 (0.60, 0.77)
Model 2	ref.	0.82 (0.76, 0.88)	0.72 (0.65, 0.80)	0.69 (0.61, 0.78)	0.71 (0.62, 0.81)
Flavanol monomers					
No. events	670	451	398	333	279
Intake (mg/d)[1]	14 (0–21)	30 (21–46)	67 (46–116)	261 (116–282)	473 (282–916)
HR (95% CI)					
Model 1	ref.	0.83 (0.79, 0.87)	0.62 (0.55, 0.69)	0.48 (0.43, 0.54)	0.49 (0.44, 0.56)
Model 1b	ref.	0.91 (0.87, 0.96)	0.79 (0.70, 0.88)	0.71 (0.61, 0.80)	0.73 (0.65, 0.83)
Model 2	ref.	0.93 (0.88, 0.98)	0.83 (0.73, 0.93)	0.78 (0.69, 0.89)	0.77 (0.68, 0.88)
Flavanol oligo+polymers					
No. events	683	452	382	322	292
Intake (mg/d)[1]	92 (0–136)	179 (136–217)	255 (217–303)	360 (303–434)	537 (434–2254)
HR (95% CI)					
Model 1	ref.	0.66 (0.61, 0.72)	0.54 (0.50, 0.59)	0.49 (0.44, 0.55)	0.45 (0.40, 0.51)
Model 1b	ref.	0.80 (0.74, 0.87)	0.71 (0.65, 0.78)	0.67 (0.60, 0.74)	0.67 (0.59, 0.77)

Model 2	ref.	0.82 (0.75, 0.89)	0.75 (0.68, 0.82)	0.72 (0.64, 0.81)	0.69 (0.61, 0.78)
Anthocyanins					
No. events	566	392	364	424	385
Intake (mg/d)[1]	5 (0–10)	13 (10–17)	20 (17–24)	36 (24–53)	71 (53–397)
HR (95% CI)					
Model 1	ref.	0.66 (0.60, 0.72)	0.57 (0.52, 0.64)	0.63 (0.56, 0.70)	0.70 (0.62, 0.79)
Model 1b	ref.	0.81 (0.74, 0.88)	0.76 (0.68, 0.85)	0.79 (0.71, 0.88)	0.81 (0.72, 0.92)
Model 2	ref.	0.84 (0.77, 0.92)	0.80 (0.72, 0.90)	0.83 (0.74, 0.94)	0.85 (0.75, 0.97)
Flavanones					
No. events	523	420	398	351	439
Intake (mg/d)[1]	3 (0–6)	9 (6–13)	18 (13–26)	32 (26–49)	70 (49–564)
HR (95% CI)					
Model 1	ref.	0.82 (0.76, 0.89)	0.70 (0.62, 0.80)	0.69 (0.61, 0.77)	0.77 (0.68, 0.86)
Model 1b	ref.	0.92 (0.85, 0.99)	0.85 (0.75, 0.96)	0.83 (0.74, 0.93)	0.90 (0.80, 1.01)
Model 2	ref.	0.93 (0.86, 1.01)	0.88 (0.78, 1.00)	0.89 (0.79, 1.00)	0.94 (0.82, 1.06)
Flavones					
No. events	554	456	376	341	404
Intake (mg/d)[1]	2 (0–3)	4 (3–4)	5 (4–6)	7 (6–9)	11 (9–51)
HR (95% CI)					
Model 1	ref.	0.70 (0.63, 0.77)	0.63 (0.57, 0.70)	0.59 (0.53, 0.65)	0.63 (0.56, 0.71)
Model 1b	ref.	0.85 (0.77, 0.94)	0.80 (0.72, 0.89)	0.76 (0.68, 0.85)	0.81 (0.72, 0.91)
Model 2	ref.	0.89 (0.80, 0.98)	0.85 (0.76, 0.95)	0.81 (0.72, 0.91)	0.90 (0.79, 1.02)

Hazard ratios (95% CI) for peripheral artery disease hospitalizations during 23 years of follow up, obtained from restricted cubic splines based on Cox proportional hazards models. Model 1 adjusted for age and sex; Model 1b adjusted for age, sex, BMI, smoking status, physical activity, alcohol intake, and socio-economic status (income); Model 2 adjusted for all covariates in Model 1b plus energy intake and intakes of fish, red meat, processed food, polyunsaturated fatty acids, monounsaturated fatty acids, and saturated fatty acids.

[1]Median; range in parentheses (all such values).

Table 3. Hazard ratios of peripheral arterial disease hospitalizations by quintiles of flavonoid compound intakes

	Flavonoid intake quintiles				
	Q1 (n=11130)	**Q2 (n=11129)**	**Q3 (n=11130)**	**Q4 (n=11129)**	**Q5 (n=11129)**
Flavonols					
Kaempferol					
No. events	674	451	388	335	283
Intake (mg/d)[1]	1 (0–1)	2 (1–3)	4 (3–8)	18 (8–20)	33 (20–68)
HR (95% CI)					
Model 1	ref.	0.82 (0.78, 0.86)	0.57 (0.51, 0.65)	0.50 (0.44, 0.56)	0.47 (0.41, 0.54)
Model 2	ref.	0.89 (0.85, 0.94)	0.74 (0.65, 0.84)	0.73 (0.64, 0.82)	0.70 (0.62, 0.80)
Model 3	ref.	0.91 (0.87, 0.96)	0.79 (0.70, 0.89)	0.78 (0.68, 0.88)	0.76 (0.67, 0.87)
Quercetin					
No. events	689	446	404	312	280
Intake (mg/d)[1]	12 (0–16)	20 (16–24)	29 (24–37)	46 (37–58)	78 (58–168)
HR (95% CI)					
Model 1	ref.	0.70 (0.66, 0.76)	0.55 (0.50, 0.60)	0.47 (0.42, 0.53)	0.45 (0.40, 0.51)
Model 2	ref.	0.81 (0.75, 0.87)	0.70 (0.64, 0.77)	0.66 (0.59, 0.74)	0.67 (0.59, 0.76)
Model 3	ref.	0.82 (0.76, 0.88)	0.72 (0.65, 0.80)	0.70 (0.62, 0.79)	0.71 (0.63, 0.82)
Flavanol monomers					
Epicatechin					

No. events	666	480	396	308	281
Intake (mg/d)[1]	6 (0–9)	12 (9–15)	19 (15–25)	31 (25–39)	53 (39–155)
HR (95% CI)					
Model 1	ref.	0.69 (0.64, 0.75)	0.54 (0.49, 0.60)	0.47 (0.42, 0.52)	0.45 (0.40, 0.51)
Model 2	ref.	0.82 (0.76, 0.88)	0.72 (0.65, 0.79)	0.67 (0.60, 0.75)	0.67 (0.59, 0.76)
Model 3	ref.	0.84 (0.78, 0.91)	0.76 (0.68, 0.84)	0.72 (0.64, 0.81)	0.73 (0.64, 0.83)
Flavanol oligo+polymers					
Procyanidin dimers					
No. events	674	447	389	324	297
Intake (mg/d) [1]	25 (0–37)	49 (38–62)	78 (62–94)	113 (94–138)	177 (138–510)
HR (95% CI)					
Model 1	ref.	0.68 (0.63, 0.73)	0.54 (0.49, 0.59)	0.50 (0.45, 0.56)	0.47 (0.41, 0.53)
Model 2	ref.	0.81 (0.75, 0.88)	0.72 (0.65, 0.79)	0.69 (0.62, 0.78)	0.66 (0.58, 0.75)
Model 3	ref.	0.84 (0.77, 0.91)	0.76 (0.68, 0.83)	0.74 (0.66, 0.83)	0.72 (0.63, 0.82)
Procyanidin trimers					
No. events	656	458	355	371	291
Intake (mg/d)[1]	10 (0–14)	17 (14–20)	23 (20–29)	35 (29–42)	54 (42–320)
HR (95% CI)					
Model 1	ref.	0.68 (0.63, 0.72)	0.55 (0.50, 0.60)	0.50 (0.45, 0.56)	0.49 (0.43, 0.55)

Model 2	ref.	0.82 (0.76, 0.88)	0.72 (0.66, 0.79)	0.65 (0.58, 0.73)	0.61 (0.54, 0.69)
Model 3	ref.	0.84 (0.78, 0.90)	0.75 (0.68, 0.82)	0.68 (0.61, 0.77)	0.65 (0.57, 0.75)
Flavanones					
Hesperidin					
No. events	512	432	388	360	439
Intake (mg/d)[1]	2 (0–4)	6 (4–9)	12 (9–18)	24 (18–38)	54 (38–449)
HR (95% CI)					
Model 1	ref.	0.83 (0.76, 0.90)	0.72 (0.64, 0.81)	0.71 (0.64, 0.80)	0.77 (0.68, 0.87)
Model 2	ref.	0.92 (0.85, 1.00)	0.87 (0.77, 0.98)	0.86 (0.77, 0.96)	0.91 (0.80, 1.02)
Model 3	ref.	0.94 (0.87, 1.02)	0.90 (0.80, 1.02)	0.89 (0.80, 1.01)	0.96 (0.85, 1.09)
Flavones					
Apigenin					
No. events	545	443	405	336	402
Intake (mg/d)[1]	2 (0–2)	3 (2–4)	5 (4–5)	6 (5–8)	10 (8–46)
HR (95% CI)					
Model 1	ref.	0.80 (0.74, 0.87)	0.68 (0.62, 0.75)	0.62 (0.56, 0.69)	0.67 (0.60, 0.75)
Model 2	ref.	0.91 (0.84, 0.99)	0.83 (0.76, 0.92)	0.78 (0.70, 0.87)	0.84 (0.74, 0.94)
Model 3	ref.	0.93 (0.85, 1.01)	0.87 (0.78, 0.96)	0.83 (0.74, 0.93)	0.92 (0.81, 1.05)
Anthocyanins					
Cyanidin					

No. events	552	396	364	384	435
Intake (mg/d)[1]	1 (0–1)	1 (1–1)	2 (1–3)	4 (3–8)	17 (8–203)
HR (95% CI)					
Model 1	ref.	0.71 (0.67, 0.76)	0.58 (0.52, 0.65)	0.61 (0.55, 0.67)	0.82 (0.71, 0.94)
Model 2	ref.	0.84 (0.79, 0.90)	0.75 (0.68, 0.84)	0.77 (0.70, 0.86)	0.90 (0.79, 1.04)
Model 3	ref.	0.87 (0.82, 0.93)	0.81 (0.72, 0.90)	0.83 (0.74, 0.92)	0.96 (0.83, 1.10)
Delphinidin					
No. events	561	354	424	350	442
Intake (mg/d)[1]	0 (0–1)	1 (1–1)	2 (1–4)	5 (4–8)	18 (8–188)
HR (95% CI)					
Model 1	ref.	0.72 (0.66, 0.78)	0.60 (0.54, 0.68)	0.66 (0.59, 0.74)	0.86 (0.76, 0.98)
Model 2	ref.	0.83 (0.76, 0.90)	0.75 (0.66, 0.85)	0.78 (0.70, 0.88)	0.89 (0.78, 1.01)
Model 3	ref.	0.84 (0.77, 0.91)	0.77 (0.68, 0.87)	0.81 (0.72, 0.91)	0.93 (0.81, 1.05)
Malvidin					
No. events	661	567	234	330	339
Intake (mg/d)[1]	0 (0–1)	2 (1–6)	6 (6–6)	11 (6–14)	36 (14–114)
HR (95% CI)					
Model 1	ref.	0.77 (0.73, 0.82)	0.54 (0.48, 0.61)	0.54 (0.49, 0.61)	0.56 (0.48, 0.64)
Model 2	ref.	0.86 (0.80, 0.91)	0.69 (0.61, 0.77)	0.68 (0.60, 0.76)	0.61 (0.51, 0.72)

Model 3	ref.	0.86 (0.81, 0.92)	0.70 (0.62, 0.79)	0.69 (0.61, 0.78)	0.62 (0.52, 0.74)

Hazard ratios (95% CI) for peripheral artery disease hospitalizations during 23 years of follow-up, obtained from restricted cubic splines based on Cox proportional hazards models. Model 1 adjusted for age and sex; Model 2 adjusted for age, sex, BMI, smoking status, physical activity, alcohol intake, and socio-economic status (income); Model 3a adjusted for all covariates in Model 3 plus intakes of fish, red meat, processed food, polyunsaturated fatty acids, monounsaturated fatty acids, and saturated fatty acids. [1]Median; range in parentheses (all such values).

FIGURE LEGENDS

Figure 1. Cubic spline curves describing the association between total flavonoid intake and both total peripheral artery disease (PAD) hospitalization events and subtypes of PAD (n=55 647). Hazard ratios and 95% CI's are based on Cox proportional hazards models adjusted for age, sex, BMI, smoking status, physical activity, social economic status (income), and alcohol intake (Model 1b) and are comparing the specific level of flavonoid intake (horizontal axis) to the median intake for participants in the lowest intake quintile (174 mg/day). Compared to a total flavonoid intake of 174 mg/d, an intake of 1000 mg/d was associated with a 32% lower risk of PAD [HR (95% CI)] [0.68 (0.60, 0.77)], a 26% lower risk of atherosclerosis [0.74 (0.62, 0.88)], a 28% lower risk of an aneurysm [0.72 (0.59, 0.88)], a non-significant 27% lower risk of an arterial embolism or thrombosis [0.73 (0.46, 1.13)], and a 47% lower risk of a hospitalization for other PVD [0.53 (0.42, 0.67)].

PVD, peripheral vascular disease (predominantly intermittent claudication).

Figure 2. Cubic spline curves describing the association between total flavonoid intake and both total peripheral artery disease-related procedures (revascularizations/endovascular surgery and amputations) in 55 572 participants of the Danish Diet Cancer and Health cohort. Hazard ratios and 95% CI's are based on Cox proportional hazards models adjusted for age, sex, BMI, smoking status, physical activity, social economic status (income), and alcohol intake (Model 1b) and are comparing the specific level of flavonoid intake (horizontal axis) to the median intake for participants in the lowest intake quintile (174 mg/day). Compared to a total flavonoid intake of 174 mg/d, an intake of 1000 mg/d was associated with a 43% lower risk of

revascularizations/endovascular surgery [HR: 0.57 (95% CI 0.46, 0.69)], and an intake of 500 mg/d was associated with a 44% lower risk of an amputation [HR: 0.56 (95% CI 0.43, 0.74)].

Figure 3. Hazard ratios based on cubic spline curves to describe the association between flavonoid subclass intakes (mg/day) and total peripheral artery disease hospitalizations among participants of the Danish Diet, Cancer and Health cohort (n = 55 647). Hazard ratios and 95% CI's are based on Cox proportional hazards models adjusted for age, sex, BMI, smoking status, physical activity, social economic status (income), and alcohol intake (Model 1b) and are comparing the specific level of flavonoid intake (horizontal axis) to the median intake for participants in the lowest intake quintile.

Figure 4. Hazard ratios based on cubic spline curves to describe the association between major flavonoid compound intakes and total peripheral artery disease hospitalizations among participants of the Danish Diet, Cancer and Health cohort (n = 55 647). Hazard ratios and 95% CI's are based on Cox proportional hazards models adjusted for age, sex, BMI, smoking status, physical activity, social economic status (income), and alcohol intake (Model 1b) and are comparing the specific level of flavonoid compound intake (horizontal axis) to the median intake for participants in the lowest intake quintile.

Figure 5. Multivariable-adjusted association between total flavonoid intake and total peripheral artery disease hospitalizations stratified by baseline smoking status (p for interaction = 0.32), alcohol intake (p for interaction = 0.40), BMI (p for interaction = 0.12), sex (p for interaction = 0.12), diabetes status (p for interaction < 0.01), cholesterol levels (p for interaction = 0.31), and

hypertension status p for interaction = 0.16). Hazard ratios and 95% CI's are based on Cox proportional hazards models and are comparing the specific level of flavonoid intake (horizontal axis) to the median intake for participants in the lowest intake quintile (174 mg/day). All analyses were standardized for age, sex, BMI, smoking, physical activity, social economic status (income), and alcohol intake (Model 1b).