Diet and Lifestyle as Risk Factors for Carotid Artery Disease: A Prospective Cohort Study

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Keywords

Stroke · Carotid artery disease · Atherosclerosis · Epidemiology · Diet

Abstract

Background: Stroke is one of the leading causes of death, and out of all stroke cases, 10–15% originate from a previously asymptomatic stenosis in the internal carotid artery. **Aims:** The aim of the study was to investigate whether dietary and lifestyle habits were associated with future risk of incident carotid artery disease (CAD). **Methods:** Baseline examinations on middle-aged individuals ($n = 30,447$) in the Malmö Diet and Cancer study (MDCS), a prospective cohort study, took place between 1991 and 1996 in Malmö, Sweden. Individuals with cardiovascular disease and diabetes mellitus were excluded at baseline, resulting in a total study population of 25,952 patients. Information on dietary intake was gathered through a 7-day food diary, a detailed questionnaire, and a 1-h interview. A diet quality index was calculated from adherence to recommended intake of 6 dietary components (saturated fat, polyunsaturated fat, fish and shellfish, fiber, vegetables and fruit, and sucrose). Individuals with a first registered diagnosis of CAD were identified from

the Swedish National Patient register. **Results:** During a median follow-up of 21.8 years, 469 participants (1.8%) developed CAD. The diagnosis of incident CAD was validated and confirmed in 99% of a random sample of 100 individuals. Higher intake of vegetables and fruit was associated with a trend of decreased risk of CAD in a Cox regression analysis (hazard ratio of 0.76, 95% confidence interval 0.56–1.03; $p = 0.080$). **Conclusions:** In conclusion, the present study found a trend toward a protective effect of higher intake of vegetables and fruit against incident CAD. More prospective studies investigating the association between diet and CAD and stroke are needed in order to give firm recommendations.

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Introduction

In Europe with its population of approximately 740 million inhabitants [1], around 1.6 million stroke cases occur yearly. When it comes to mortality, stroke is the second most common cause of death in Europe, accounting for 1 million deaths each year [2]. More than half of stroke survivors are dependent on others to be able to

Fig. 1. Descriptive flow diagram of study participants, dietary data, and exclusions. Some individuals had multiple exclusion criteria. CAD, carotid artery disease; CoAD, coronary artery disease; PAD, peripheral artery disease.

perform their activities of daily living [3]. Stroke generates enormous costs for health care systems in the European Union, in total around 45 billion Euros every year [2].

Overall, 10–15% of all stroke cases originate from a previously asymptomatic stenosis (>50%) in the internal carotid artery [4]. In addition, presence of atherosclerosis in the internal carotid artery has been shown to be an independent risk factor for cardiovascular (CV) events [5].

Guidelines for managing CV diseases [6] often highlight the importance of healthy dietary habits and other lifestyle factors, being modifiable risk factors for CV disease. Lack of a high intake of vegetables and fruit is a contributing risk factor to the development of hypertension and its complications [7]. However, the association between nutrients and lifestyle factors and development of carotid artery disease (CAD) has been scarcely studied.

The purpose of this population-based prospective longitudinal study was to evaluate whether dietary habits and lifestyle are associated with future risk of incident CAD. The results can potentially improve our understanding of the role of diet in CAD and ischemic stroke. The study hypothesis was that there would be an inverse association between healthy diet and incident CAD.

Methods

Study Population and Data Collection

Men born 1923–1945 and women born 1923–1950 living in Malmö were eligible to enter the Malmö Diet and Cancer study (MDCS) and baseline examinations were carried out between 1991 and 1996 [8]. Individuals who underwent dietary assessment were included, whereas individuals with prevalent CV disease were excluded. The cohort was designed to study dietary habits, and individuals who more likely might have changed the dietary habits during follow-up, such as patients with known diabetes mellitus and CV disease, were excluded at baseline (Fig. 1).

Diet Assessment Method and Diet Quality Index

Information on dietary habits was collected through a 7-day food diary, where the participants recorded their food intake at lunch and dinner meals and intake of cold beverages, together with a 168-item food frequency questionnaire, where frequency and portion size of foods regularly consumed during the past year were documented [9]. The participants underwent a 1-h interview, where further details were collected. A diet quality index has previously been developed and validated within the MDCS cohort [10]. The index is based on the Swedish nutrition recommendations [11] for consumption of 6 dietary components: saturated fat ≤ 14 energy (E)%, polyunsaturated fat 5–10 E%, fish and shellfish ≥ 300 g/week, sucrose ≤ 10 E%, dietary fiber ≥ 2.4 g/MJ or ≥ 1 g/100 kcal, and fruit and vegetables ≥ 400 g/day. E% refers to daily energy percentage derived from each energy nutrient. Individuals who reached the recommendations were given 1 point for each component, with a maximum score of 6 points [10].

Lifestyle and Other Variables

Hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or antihypertensive drug treatment. We have chosen to not include intermediary factors such as hypertension in the multivariable statistical models. Hypertension was nevertheless added in a sensitivity analysis in the final mutually adjusted multivariable statistical model. A smoking score was established, ranging from 0 (no smoking) to 4 (current smoking). Alcohol consumption was stratified into 6 groups. Education level was divided into 5 categories. Leisure-time physical activity level was expressed as metabolic equivalent of task hours per week based on intensity level and time spent on 17 different activities and was divided into 5 groups.

Endpoint Ascertainment

The MDCS cohort was followed from baseline (1991–1996) until 31 December 2016. Individuals with a first registered diagnosis of CAD were identified from the Swedish National Patient register and the Cause of Death Register by using the participants' civic registration numbers. Diagnoses are coded using a Swedish revision of the International Classification of Disease (ICD), version 8 (432.00; 432.90), version 9 (443B), and version 10 (I65.2). CAD was defined by whenever the code for CAD first was registered, and symptomatic CAD when there was a $\geq 60\%$ stenosis of the internal carotid artery on color Doppler ultrasound judged as responsible for an associated clinical event.

Validation of CAD Diagnosis

One hundred patients with a diagnosis of CAD (ICD 10; I65.2) were randomly selected for the validation procedure using patient record data. Among 100 patients, 57 had symptomatic ($\geq 60\%$ stenosis of the internal carotid artery on color Doppler ultrasound) CAD and 42 had asymptomatic CAD. The proportion of operated patients with symptomatic and asymptomatic ($\geq 70\%$) CAD was 85.9% (49/57) and 14.3% (6/42), respectively. One patient had coronary artery disease and was misdiagnosed. The diagnosis of CAD was therefore confirmed in 99% of the validation sample and symptomatic CAD in 57%.

Statistical Analysis

Baseline characteristics were expressed as median and interquartile range (IQR) or mean and standard deviation (SD) for continuous variables, and as total count and percentage for categorical variables. In order to address confounding in baseline characteristics, hazard ratios (HRs) with 95% CI were calculated using the Cox regression analysis. The time scale was defined as years of follow-up. HRs for hypertension and lifestyle factors were adjusted for age and sex. HRs for diet variables were adjusted for age, sex, diet assessment method, season, and energy intake. HRs were calculated for adherence to each dietary recommendation. These variables were adjusted for age, sex, total energy intake, diet assessment method, and season in the basic model. In the multivariable model, the modifiable variables such as alcohol consumption, physical activity, smoking status, education level, and BMI were added. Each of the 6 dietary components included in the mutually adjusted model were adjusted for the variables in the multivariable model, as well as for the remaining 5 diet quality index components. Statistical analyses were performed using IBM SPSS Statistics, version 26 (SPSS, Chicago, IL, USA), and the chosen level of statistical significance was $p < 0.05$.

Results

Demographic Baseline Characteristics

During a median of 21.8 years (IQR 4.9) of follow-up, 469 out of 25,952 (1.8%) patients were diagnosed with CAD. Baseline characteristics of those who developed CAD and those who did not are presented in Table 1. Individuals with hypertension had a higher risk for CAD (HR 2.20, 95% CI: 1.78–2.72; $p < 0.001$). There was an increased risk for CAD among those who recently quit smoking (HR 1.52, 95% CI: 1.12–2.07; $p = 0.007$). A higher proportion of participants in the 2 quintiles with lower alcohol intake were seen in the group with no CAD.

Adherence to Diet Quality Index Components and CAD Risk

Individuals who adhered to the recommended intakes of the 6 different diet components did not show a significantly lower risk of CAD in the basic model or the multivariable model. 897 (3.5%) and 770 (3.0%) individuals had the highest (6) and the lowest (0) scores, respectively. There was no clear association between high diet score and incidence of CAD in the basic model (HR = 0.954, 95% CI: 0.893–1.020; $p = 0.169$), the multivariable model (HR = 0.969, 95% CI: 0.904–1.038; $p = 0.367$), or the mutually adjusted multivariable model (HR = 0.908, 95% CI: 0.811–1.017; $p = 0.095$). There was a trend of decreased risk for reached recommendation of vegetables and fruit (HR 0.76, 95% CI: 0.56–1.03; $p = 0.080$) in the mutually adjusted multivariable model, but not for fiber intake (HR 0.77, 95% CI: 0.56–1.06; $p = 0.105$) (Table 2).

In a sensitivity analysis, hypertension was added into the mutually adjusted multivariable model, still resulting in a trend (HR 0.75, 95% CI: 0.55–1.02; $p = 0.069$) for association between reached recommendation for vegetables and fruit and incident CAD. Hypertension was found to be an independent variable associated with incident CAD in the same model (HR 2.15, 95% CI: 1.73–2.66; $p < 0.001$).

Discussion

The main finding in this population-based prospective cohort study with a median follow-up of 21.8 years was a trend toward a protective effect of adherence to recommended levels of fruit and vegetable on risk of incident CAD. Similarly, fruit and vegetables have been found to reduce the incidence of peripheral artery disease [12], CV events [13], and abdominal aortic aneurysm [14] in the

Table 1. Baseline characteristics of study participants with and without incident CAD in the MDCS cohort

	Incident CAD (<i>n</i> = 469)	No CAD (<i>n</i> = 25,483)	<i>p</i> value	HR (95% CI)
Male sex, <i>n</i> (%)	176 (37.5)	9,972 (39.1)	0.489	0.94 (0.78–1.13)
Age, years	56.5 (12.7)	57.8 (13.1)	0.029	0.99 (0.98–1.00)
Total energy intake, kcal/day	2,297.6 (618.1)	2,271.9 (653.5)	0.388	1.00 (1.00–1.00)
BMI, kg/m ²	25.0 (3.8)	25.8 (4.0)	<0.001	0.95 (0.93–0.98)
Hypertension, %	353 (75.4)	15,346 (60.4)	<0.001	2.20 (1.78–2.72)
<i>Alcohol consumption, n (%)</i>				
Zero-consumers	42 (9)	1,644 (6.5)	0.176	1 (ref)
<0.9, g/day for women/<3.4, g/day for men	73 (15.6)	4,766 (18.7)	0.007	0.59 (0.41–0.87)
0.9–4.3, g/day for women/3.4–9.1, g/day for men	85 (18.1)	4,794 (18.8)	0.046	0.69 (0.47–0.99)
4.4–8.1, g/day for women/9.2–15.7, g/day for men	92 (19.6)	4,771 (18.7)	0.116	0.75 (0.52–1.08)
8.2–14.0, g/day for women/15.7–25.7, g/day for men	86 (18.3)	4,767 (18.7)	0.044	0.68 (0.47–0.99)
>14.0, g/day for women/>25.7, g/day for men	91 (19.4)	4,741 (18.6)	0.069	0.71 (0.49–1.03)
<i>Smoking score, n (%)</i>				
Never	165 (37.0)	9,969 (41.1)	0.096	1 (ref)
No smoking since 25–51 years	43 (9.6)	2,626 (10.8)	0.820	1.04 (0.74–1.46)
No smoking since 12–24 years	67 (15.0)	3,306 (13.6)	0.175	1.22 (0.92–1.63)
No smoking since 1–11 years	55 (12.3)	2,202 (9.1)	0.007	1.52 (1.12–2.07)
Currently smoking	116 (26.0)	6,158 (25.4)	0.397	1.11 (0.87–1.41)
<i>Leisure-time physical activity, n (%)</i>				
<7.5 MET-h/week	34 (7.3)	2,476 (9.8)	0.340	1 (ref)
7.5–15.0 MET-h/week	76 (16.2)	3,785 (15.0)	0.067	1.46 (0.97–2.19)
15.1–25.0 MET-h/week	106 (22.6)	5,817 (23.0)	0.163	1.32 (0.89–1.94)
25.1–50.0 MET-h/week	170 (36.3)	9,174 (36.3)	0.102	1.36 (0.94–1.97)
>50.0 MET-h/week	82 (17.5)	4,051 (16.0)	0.046	1.50 (1.01–2.24)
<i>Educational level, n (%)</i>				
Less than 9 years	181 (38.6)	10,663 (42.0)	0.582	1 (ref)
Elementary school (9–10 yr)	132 (28.1)	6,638 (26.1)	0.328	1.12 (0.89–1.41)
Elementary + upper secondary school (9–13 yr)	50 (10.7)	2,258 (8.9)	0.196	1.23 (0.90–1.41)
University studies, no degree	37 (7.9)	2,238 (8.8)	0.653	0.92 (0.65–1.32)
University studies, with degree	69 (14.7)	3,621 (14.2)	0.757	1.05 (0.79–1.39)
<i>Dietary components</i>				
Saturated fat, E%	16.36 (3.88)	16.16 (3.80)	0.399	1.01 (0.99–1.04)
Polyunsaturated fat, E%	5.98 (1.52)	5.94 (1.56)	0.635	1.01 (0.98–1.08)
Sucrose, E%	8.59 (3.33)	8.50 (3.54)	0.738	1.00 (0.98–1.03)
Fiber, g/MJ	2.19 (0.64)	2.22 (0.65)	0.410	0.94 (0.81–1.09)
Vegetables and fruit, g/1,000 kcal	338.02 (206.37)	347.21 (230.08)	0.646	1.00 (1.00–1.00)
Fish and shellfish, g/week	277.00 (290.18)	277.09 (290.01)	0.790	1.00 (1.00–1.00)

Data are *n* (%), mean (SD), or median (IQR). HR for hypertension and lifestyle factors adjusted for age and sex; HR for diet variables adjusted for age, sex, diet assessment method, season, and energy intake. E, energy; MET, metabolic equivalent of task; MJ, megajoules; CAD, carotid artery disease; IQR, interquartile range; HR, hazard ratio.

same cohort. Only one other prospective longitudinal cohort study was found to specifically address the association between intake of vegetables and CAD, which showed an inverse association of vegetable nitrate intake with carotid atherosclerosis and ischemic cerebrovascular disease in older women after a follow-up of 14.5 years [15].

One randomized controlled trial aiming at reducing total fat intake and encouraging increased fruit, vegetables, and grains showed no change in the risk for incident CAD at 8.3 years of follow-up among postmenopausal women [16]. The study was originally designed to test the hypothesis that dietary intervention would reduce CV disease

Table 2. HR and 95% CI for incident CAD by adherence to diet quality index components

Dietary components	Nonadherence	Adherence
Saturated fat, %	≥14 E	≤14 E
Incident CAD	141/8,011	364/19,139
Basic model ^a	1.00 (1.00–1.00)	0.92 (0.75–1.13)
Multivariable model ^b	1.00 (1.00–1.00)	0.96 (0.77–1.18)
Mutually adjusted multivariable model ^c	1.00 (1.00–1.00)	0.97 (0.72–1.29)
Polyunsaturated fat, %	<5 E or >10 E	5–10 E
Incident CAD	357/18,778	148/8,372
Basic model ^a	1.00 (1.00–1.00)	1.10 (0.90–1.35)
Multivariable model ^b	1.00 (1.00–1.00)	1.09 (0.89–1.34)
Mutually adjusted multivariable model ^c	1.00 (1.00–1.00)	1.08 (0.85–1.38)
Sucrose, %	≥10 E	≤10 E
Incident CAD	150/7,626	355/19,524
Basic model ^a	1.00 (1.00–1.00)	0.91 (0.75–1.11)
Multivariable model ^b	1.00 (1.00–1.00)	0.93 (0.76–1.14)
Mutually adjusted multivariable model ^c	1.00 (1.00–1.00)	0.84 (0.61–1.15)
Fiber, g/MJ	≤2.4	≥2.4
Incident CAD	353/18,075	152/9,075
Basic model ^a	1.00 (1.00–1.00)	0.84 (0.69–1.03)
Multivariable model ^b	1.00 (1.00–1.00)	0.86 (0.70–1.07)
Mutually adjusted multivariable model ^c	1.00 (1.00–1.00)	0.77 (0.56–1.06)
Vegetables and fruit, g/day	≤400	≥400
Incident CAD	320/16,819	185/10,331
Basic model ^a	1.00 (1.00–1.00)	0.88 (0.72–1.06)
Multivariable model ^b	1.00 (1.00–1.00)	0.90 (0.74–1.10)
Mutually adjusted multivariable model ^c	1.00 (1.00–1.00)	0.76 (0.56–1.03)
Fish, g/week	≤300	≥300
Incident CAD	279/14,722	226/12,428
Basic model ^a	1.00 (1.00–1.00)	0.97 (0.81–1.17)
Multivariable model ^b	1.00 (1.00–1.00)	1.00 (0.82–1.21)
Mutually adjusted multivariable model ^c	1.00 (1.00–1.00)	0.92 (0.69–1.21)

CAD, carotid artery disease; HR, hazard ratio. ^a Basic model: adjusted for age, sex, and total energy intake. ^b Multivariable model: adjusted for age, sex, total energy intake, alcohol consumption, physical activity, smoking, education, and BMI. ^c Mutually adjusted multivariable model: adjusted for age, sex, total energy intake, alcohol consumption, physical activity, smoking, education, BMI, and mutual adjustment for the 6 diet quality index components.

defined as coronary heart disease and stroke, and were thus beforehand underpowered to investigate the association between the dietary intervention and risk for CAD. In another randomized clinical trial involving 175 subjects at high CV risk adhered to a Mediterranean diet rich in plant-derived foods and whole grain, a regression or delayed progression of internal carotid artery intima thickness, carotid plaques, and atherosclerosis in general was found at 2.4 years of follow-up [17]. Patients with CAD and other atherosclerotic diseases have a high long-term all-cause and cardiac-related mortality [18] and ev-

idence points to a diet rich in plant foods playing a major role in preventing atherosclerotic development regardless of localization in the vascular tree.

Several mechanisms have been suggested to explain the effect of plant foods on atherosclerotic development. Vitamin C has been shown to restore endothelial function through improved perfusion in atherosclerotic sites of vessels, hindering the atherosclerotic process. Another study on the MDCS cohort found vegetables and fruit to be protective against AAA. Fruit and vegetables are rich in antioxidants, which are believed to inhibit oxidative

stress in the aortic wall, thereby reducing AAA progression. Furthermore, inorganic nitrate found in green leafy vegetables has been shown to act in a protective way, reducing high blood pressure and plaque development [14]. The fact that individuals with a higher intake of vegetables and fruit also may lead a healthier lifestyle in general, decreasing the risk of CV disease, should also be taken into consideration.

There is a risk of self-reported dietary and lifestyle habits being misreported to some extent, and these habits might have changed at follow-up. It is, however, unlikely that the middle-aged study participants markedly changed their dietary habits in their later stage of life. In a longitudinal study following middle-aged individuals attempting fat reduction showed that almost 70% had not altered their diet after 24 months [19]. In addition, individuals who might have altered their diet due to diabetes and CV disease were excluded at baseline. Moreover, the dietary assessment methods used have been shown to have high validity [10]. Furthermore, it could have been of value to perform ultrasound examinations at baseline and at follow-up in order to identify cases of asymptomatic CAD. Thereby patients with prevalent asymptomatic CAD could have been excluded at baseline, and also given a larger sample size of individuals with incident CAD at follow-up. Accuracy of data would have improved, and a larger endpoint sample size would have increased statistical power and reducing the risk of type 2 statistical error, perhaps turning trends to significant results.

The main strengths of the present study are the large sample size and the follow-up time of over 20 years. These are strong methodological factors making it possible to follow the middle-aged participants into older age, where the incidence of CAD peaks [20]. Registries were used to attain disease endpoints, which poses another significant strength as it ensured almost complete follow-up of the study participants. Furthermore, the validity of the CAD diagnosis was high, with confirmation of the diagnosis in 99% of the validation sample.

A systematic review of 20 studies found a general trend between diets rich in plant foods and decreased carotid intima thickness [21]. The study emphasized the need for long-term prospective studies on large populations to further investigate the effects of dietary patterns on CAD, which highlights the value of the present study.

In conclusion, the present study found a trend toward a protective effect of higher intake of vegetables and fruit against incident CAD. More prospective studies investigating the association between diet and CAD and stroke are needed to be able to give firm recommendations.

Statement of Ethics

The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written and oral informed consent was obtained from the study participants and ethical clearance was obtained from the Regional Ethical Review Board in Lund, Sweden (Dnr § LU 51-90, 2007/166).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.A. and A.J. conceived of the concept and design of the work. S.A. and A.J. performed the analysis and interpretation of data. A.J. drafted the work. S.A. revised it critically and approved the final version to be published. A.J. and S.A. agreed to be accountable for all aspects of the work.

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