ORIGINAL RESEARCH

Cruciferous and Total Vegetable Intakes Are Inversely Associated With Subclinical Atherosclerosis in Older Adult Women

Lauren C. Blekkenhorst, BHSc; Catherine P. Bondonno, PhD; Joshua R. Lewis, PhD; Richard J. Woodman, PhD; Amanda Devine, PhD; Nicola P. Bondonno, BSc; Wai H. Lim, MD, PhD; Kun Zhu, PhD; Lawrence J. Beilin, MD; Peter L. Thompson, MD; Richard L. Prince, MD; Jonathan M. Hodgson, PhD

***Background*—**Dietary patterns rich in fruits and vegetables are considered to reduce atherosclerotic disease presentation and are reported to be inversely associated with subclinical measures of atherosclerosis, such as carotid artery intima-media thickness (IMT) and plaque. However, the effect of vegetable intake alone, and relationships to specific types of vegetables containing different phytochemical profiles, is important. The aim of this study was to investigate the associations of total vegetable intake and specific vegetables grouped according to phytochemical constituents with common carotid artery IMT (CCA-IMT) and carotid plaque severity in a cohort of older adult women (aged ≥70 years).

***Methods and Results*—**Total vegetable intake was calculated at baseline (1998) using a validated food frequency questionnaire. Vegetable types included cruciferous, allium, yellow/orange/red, leafy green, and legumes. In 2001, CCA-IMT (n=954) and carotid focal plaque (n=968) were assessed using high-resolution B-mode carotid ultrasonography. Mean (SD) total vegetable intake was 199.9 (78.0) g/d. Women consuming ≥3 servings of vegetables each day had ≈4.6% to 5.0% lower mean CCA-IMT (P=0.014) and maximum CCA-IMT (P=0.004) compared with participants consuming <2 servings of vegetables. For each 10 g/d higher in cruciferous vegetable intake, there was an associated 0.006 mm (0.8%) lower mean CCA-IMT (P<0.01) and 0.007 mm (0.8%) lower maximum CCA-IMT (P<0.01). Other vegetable types were not associated with CCA-IMT (P>0.05). No associations were observed between vegetables and plaque severity (P>0.05).

***Conclusions*—**Increasing vegetables in the diet with a focus on consuming cruciferous vegetables may have benefits for the prevention of subclinical atherosclerosis in older adult women.

***Clinical Trial Registration*—**URL: http://www.anzctr.org.au. Unique identifier: ACTRN12615000750583. **(*J Am Heart Assoc.* 2018;7:e008391. DOI: 10.1161/JAHA.117.008391.)**

Key Words: atherosclerosis • carotid intima-media thickness • carotid plaque • cruciferous • vegetables

Higher vegetable intake is consistently associated with a reduced risk of coronary heart disease and stroke.[1] The underlying cause of these cardiovascular disease subgroups is atherosclerosis, a complex multifactorial disorder of the arteries initiated by endothelial dysfunction, inflammation, and dyslipidemia.[2,3] Subclinical measures of atherosclerosis include common carotid artery intima-media thickness (CCA-IMT) and carotid atherosclerotic plaques, both of which have been shown to predict myocardial infarction and stroke.[4–6]

Diets high in vegetables, such as the Mediterranean-style diet and the vegetarian diet, have been shown to be associated with lower CCA-IMT[7,8] and delayed progression of atherosclerotic plaques.[9] However, the role of individual dietary components, such as vegetables, is uncertain.[10]

From the School of Medical and Health Sciences, Edith Cowan University, Joondalup, Western Australia, Australia (L.C.B., C.P.B., J.R.L., A.D., J.M.H.); Medical School, Royal Perth Hospital Unit, University of Western Australia, Perth, Western Australia, Australia (L.C.B., C.P.B., N.P.B., L.J.B., J.M.H.); Medical School, Queen Elizabeth Medical Centre Unit, University of Western Australia, Nedlands, Western Australia, Australia (L.C.B., J.R.L., R.L.P.); Centre for Kidney Research, Children's Hospital at Westmead, New South Wales, Australia (J.R.L.); School of Public Health, Sydney Medical School, University of Sydney, New South Wales, Australia (J.R.L.); Flinders Centre for Epidemiology and Biostatistics, Flinders University, Adelaide, South Australia, Australia (R.J.W.); and Departments of Renal Medicine (W.H.L.), Endocrinology and Diabetes (K.Z., R.L.P.), and Cardiovascular Medicine (P.L.T.), Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia.

Correspondence to: Lauren C. Blekkenhorst, BHSc, Medical School, Royal Perth Hospital Unit (M570), The University of Western Australia, 35 Stirling Hwy, Crawley, Western Australia 6009, Australia. E-mail: lauren.blekkenhorst@research.uwa.edu.au

Received January 16, 2018; accepted February 13, 2018.

Clinical Perspective

What Is New?

- In a cohort of older Australian women, a higher intake of vegetables (≥225 g/d in comparison to <150 g/d) was associated with a ≈5% lower common carotid artery intima-media thickness.
- Cruciferous vegetables, including cabbage, brussels sprouts, cauliflower, and broccoli, contributed the most towards this beneficial effect.

What Are the Clinical Implications?

- Cruciferous vegetables are recognized to be a good source of several nutrients and bioactive phytochemicals.
- This observational cohort study provides evidence of a vascular protective effect.
- If supported by other studies, dietary guidelines should highlight the importance of increasing consumption of cruciferous vegetables for protection from vascular disease.

Furthermore, given the heterogeneity of vegetables, there has been little research investigating whether specific types of vegetables are associated with a reduction in atherosclerosis.

Vegetables contain many nutrients and bioactive compounds, such as phytochemicals that may slow the progression of atherosclerosis.[11] Some of these naturally occurring compounds include carotenoids, polyphenols, organosulfur compounds, and nitrogen-containing compounds.[12–15] Different types of vegetables contain different levels of these putative protective components. For example, cruciferous vegetables, such as cabbage, brussels sprouts, cauliflower, and broccoli, and allium vegetables, such as onions, leek, and garlic, are rich sources of organosulfur compounds, which are proposed to be beneficial for cardiovascular health.[14] Another example is leafy green vegetables, such as spinach and lettuce, which are a rich source of the nitrogen-containing compound, nitrate. Nitrate has been shown in clinical trials to lower blood pressure,[16,17] a major risk factor for cardiovascular disease. If specific components have a greater protective role in atherosclerosis, then particular types of vegetables rich in these components may confer a greater cardioprotective effect, as we have previously demonstrated.[18]

The primary objective of this study was to investigate the associations of total vegetable intake and intake of specific types of vegetables, grouped according to phytochemical constituents previously outlined, with CCA-IMT and carotid plaque severity in a cohort of older adult women. Because of the potential for cocorrelation, the effects of individual dietary confounders were studied.

Methods

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure. This material will be available on request and approval at http://www.lsaw.com.au/.[19]

Study Population

Participants (n=1500) for this observational study were initially enrolled in 1998 to the CAIFOS (Calcium Intake Fracture Outcome Study). The CAIFOS was a 5-year, double-blinded, randomized, placebo-controlled trial of daily calcium supplementation (1.2 g calcium carbonate) to prevent osteoporotic fracture.[20] Participants were recruited in 1998 from the Western Australian general population of women aged ≥70 years. Invitations were sent by mail using the Electoral Roll, which is maintained for all Australian citizens enrolled to vote in Western Australia. All participants recruited into the study were ambulant, with an expected survival beyond 5 years, and were not receiving any medication known to affect bone metabolism (including hormone replacement therapy). Participants were comparable in terms of disease burden and medication use to the general population of similar age but were more likely to come from a higher socioeconomic status.[21] A total of 39 of 1500 participants (2.6%) of the CAIFOS received 1.2 g calcium carbonate plus 1000 IU of vitamin D (ergocalciferol) as part of a substudy.[22] In 2001, a preplanned ancillary study was performed to investigate the epidemiological determinants of CCA-IMT and carotid atherosclerosis in 1154 of 1500 participants (77%). The remaining women (n=346) had died, withdrew from the study, or were unable to be scheduled. Both studies were approved by the Human Ethics Committee at the University of Western Australia, and written informed consents were obtained from all participants.

Inclusion criteria for the current observational study included all available exposure and outcome variables. Exclusion criteria included no dietary data, implausible energy intakes, and participants with prevalent atherosclerotic vascular disease (ASVD) or diabetes mellitus. Dietary data were available in 1146 of 1154 participants (99.3%). Implausible energy intakes (<2100 kJ [500 kcal] or >14 700 kJ [3500 kcal] per day) resulted in 12 of 1146 participants (1.0%) being excluded. Participants with prevalent ASVD (n=107), diabetes mellitus (n=44), or both (n=15) at baseline (1998) were excluded, leaving 968 participants for the carotid plaque severity analysis and 954 participants for the CCA-IMT analysis (n=14 with missing CCA-IMT data) (Figure 1). Prevalent ASVD and/or diabetes mellitus at baseline was an a priori exclusion criteria to help avoid the possibility of reverse causality, which may weaken the true association. Prevalence of ASVD at baseline (1998) was determined from principal

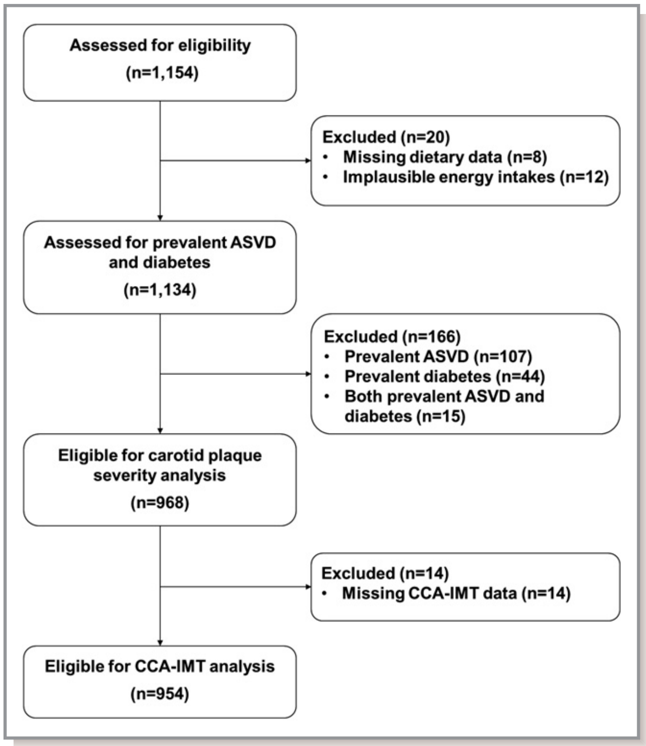

Figure 1. Participant flow chart. ASVD indicates atherosclerotic vascular disease; CCA-IMT, common carotid artery intima-media thickness.

hospital discharge diagnosis codes from 1980 to 1998 using the Hospital Morbidity Data Collection, linked via the Western Australian Data Linkage System. Diagnosis codes for ASVD included ischemic heart disease (*International Statistical Classification of Diseases, Injuries and Causes of Death, Ninth Revision* [*ICD-9*]/*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] codes 410–414); heart failure (*ICD-9/ICD-9-CM* code 428); cerebrovascular disease, excluding hemorrhage (*ICD-9/ICD-9-CM* codes 433–438); and peripheral arterial disease (*ICD-9/ICD-9-CM* codes 440–444). These codes were defined using the manual of the *ICD-9*[23] and the Australian Version of the *ICD-9-CM*.[24] Prevalent diabetes mellitus at baseline (1998) was determined using medication use. Medications were coded (T89001–T90009) using the International Classification of Primary Care—Plus method.[25]

CCA-IMT and Carotid Plaque Severity

CCA-IMT and carotid plaque severity were assessed at year 3 (2001) using high-resolution B-mode carotid ultrasonography. Ultrasounds were conducted by the same sonographer using a standard image acquisition protocol.[26] An 8.0-mHz linear array transducer attached to an Acuson Sequoia 512 ultrasound machine (Mountain View, CA) was used. To account for asymmetrical wall thickening, images were taken from 3 different angles (anterolateral, lateral, and posterolateral) of the far walls of the distal 2 cm of the left and right common carotid arteries. The same technician conducted offline analyses on all end-diastolic images using a semiautomated edge-detection software program. The mean and maximum CCA-IMT (mm) from each of the 6 images (3 on either side) were averaged to give an overall mean CCA-IMT and maximum CCA-IMT. A short-term precision study was undertaken in 20 nontrial subjects using the same sonographer and technician. Repeated IMT measurements were made between 0 and 31 days apart (mean, 10.3 days). The coefficient of variation for the repeated measures was 5.98% (calculated using the root-mean-square method).[27] Focal plaques were then determined by examining the entire carotid tree (CCA, carotid bulb, and internal and external carotid). Carotid plaque severity was categorized according to the degree of stenosis: less advanced (<25% stenosis) or more advanced (≥25% stenosis).[28]

Dietary Intake Assessment

A semiquantitative food frequency questionnaire was used to assess dietary intake at baseline (1998). This questionnaire was developed and validated by the Cancer Council of Victoria and was designed to assess usual dietary intake over a period of 12 months.[29–31] Food intake frequency was assessed by 10 frequency options, ranging from "never" to "≥3 times per day," and portion size was calculated using photographs of scaled portions of different food types. Energy and nutrient intakes were calculated by the Cancer Council of Victoria using the NUTTAB 95 food composition database[32] and were supplemented by other data where necessary. Food items (including 24 vegetable items) were individually calculated in g/d by the Cancer Council of Victoria. A research assistant supervised participants while completing the questionnaires and provided food models, photographs, measuring cups, and spoons for the accuracy of reported food consumption.

Total vegetable intake

Total vegetable intake was calculated per serving (75 g/d) on the basis of the 2013 Australian Dietary Guidelines.[33] Servings per day were then categorized into 3 categories (<2, 2–<3, and ≥3 servings/day) with a similar number of participants in each category. "Potatoes, roasted or fried, including hot chips" was not included in total intake of vegetables because hot chips are not recommended as part of a healthy diet.[33] "Potatoes cooked without fat" were included.

Vegetable types

Vegetables were grouped on the basis of the 2013 Australian Dietary Guidelines[33] and were modified relating to phytochemical constituents, as previously described.[18,34] Vegetable types included cruciferous (cabbage, brussels sprouts, cauliflower, and broccoli), allium (onion, leek, and garlic), yellow/orange/red (tomato, capsicum, beetroot, carrot, and pumpkin), leafy green (lettuce and other salad greens, celery, silver beet, and spinach), and legumes (peas, green beans, bean sprouts, alfalfa sprouts, baked beans, soy beans, soy bean curd and tofu, and other beans).

Baseline Demographic and Clinical Assessment

Body weight (in kilograms) and height (in meters) were assessed using digital scales and a wall-mounted stadiometer, respectively. Participants were wearing light clothing with no socks and shoes. Body mass index (kg/m^2) was then calculated. Questionnaires were used to assess physical activity and smoking status. Physical activity (kJ/d) was calculated using a validated method using the type of activity, time engaged in the activity, and the participants' weight.[35,36] Smoking status was coded as nonsmoker or ex-smoker/current smoker. Ex-smoker/current smoker was defined as consuming >1 cigarette/day for >3 months at any time during the participants' life. Alcohol intake (g/d) was assessed using the validated food frequency questionnaire, as previously described. Socioeconomic status was calculated using the Socioeconomic Indexes for Areas developed by the Australian Bureau of Statistics. These indexes ranked residential postcodes according to relative socioeconomic advantage and disadvantage. Participants were coded into 6 groups from the top 10% most highly disadvantaged to the top 10% least disadvantaged.[37]

A detailed medical history and list of current medications were obtained from all participants and were verified by their general practitioner, where possible. Medication use was coded using the International Classification of Primary Care—Plus method, which allows aggregation of different terms for similar pathologic entities, as defined by the *ICD-10* coding system.[25] Use of antihypertensive agents, statin therapy, and low-dose aspirin was included in the multivariable models to adjust for atherosclerotic-related risk factors, such as hypertension and dyslipidemia. Baseline serum creatinine was analyzed in 875 of 968 participants (90.4%) using an isotope dilution mass spectrometry traceable Jaffe kinetic assay and Hitachi 917 analyzer (Roche Diagnostics GmbH, Mannheim, Germany).[38] Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation[39] and was added to the multivariable-adjusted models because this has been shown to predict atherosclerotic disease in this cohort of older adult women.[38] Total cholesterol, high-density lipoprotein cholesterol, and triglyceride concentrations were analyzed in 895 of 968 participants (92.5%) using a Hitachi 917 autoanalyzer (Roche Diagnostics GmbH). Low-density lipoprotein cholesterol was calculated in 888 of 968 participants (91.7%) using the Friedewald's method.[40]

Statistical Analysis

An analytical protocol was produced before analysis. Statistical significance was set at a 2-sided type 1 error rate of $P<0.05$. All data were analyzed using IBM SPSS Statistics for Windows, version 21.0 (IBM) and SAS software, version 9.4 (SAS Institute Inc). Normality was assessed for each variable by observing whether the frequency distribution curves and quantile-quantile plots showed evidence of a normal distribution. Descriptive statistics of normally distributed continuous variables were expressed as mean$\pm$SD, nonnormally distributed continuous variables (physical activity, alcohol intake, allium vegetable intake, nut intake, fish intake, processed meat intake, and red meat intake) were expressed as median and interquartile range, and categorical variables were expressed as number and proportion (percentage). Differences in baseline characteristics and dietary intakes among vegetable serve categories were tested using 1-way ANOVA for normally distributed continuous variables and the Kruskal-Wallis test for nonnormally distributed continuous variables. The χ^2 test for independence was used to test for differences in baseline characteristics and dietary intakes for categorical variables.

Multivariate linear regression was used to investigate the association between CCA-IMT (mean and maximum) and our primary exposures of interest (total vegetable intake and intake of vegetable types). The association between focal plaque severity (less advanced versus more advanced) and the same exposure variables was investigated using binary logistic regression. Three models of adjustment were used in each analysis: unadjusted, age and energy adjusted, and multivariable adjusted (age, body mass index, level of physical activity, alcohol intake, smoking history, socioeconomic status, the CAIFOS supplementation group of calcium versus calcium plus vitamin D versus placebo, use of antihypertensive agents, statin therapy and low-dose aspirin, Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate, and energy intake). Covariates were entered into the models as continuous variables, with the exception of smoking history, socioeconomic status, the CAIFOS supplementation group of calcium versus calcium plus vitamin D versus placebo, use of antihypertensive agents, statin therapy, and low-dose aspirin, which were entered as categorical variables. When assessing the association for vegetable types, the total intake from other vegetables was added to the multivariable-adjusted model as an additional analysis. Covariates included in the adjusted models were selected on an a priori basis because of their biological relationship with cardiovascular disease.

Sensitivity analysis

In addition to the fully adjusted models, we also considered the potential for confounding from other dietary components. Given the potential for multicollinearity between many of these confounders, we considered their impact by entering them into models separately, each as a continuous variable, for mean and maximum CCA-IMT. These included daily intakes of total fruit (g/d),[41] fish (g/d), nuts (g/d), red meat intake (g/d), processed meat intake (g/d), fiber (g/d), potassium (mg/d), magnesium (mg/d), monounsaturated fat (g/d), saturated fat (g/d),[42] and vegetable-derived nitrate (mg/d).[43] In addition, because potato can be classified nutritionally as a starchy food, potatoes cooked without fat were excluded from the calculation of total vegetable intake and the fully adjusted models were reanalyzed for mean and maximum CCA-IMT. Furthermore, vitamin D has been associated with subclinical atherosclerosis[44]; we therefore excluded participants who had received 1.2 g calcium carbonate plus 1000 IU of vitamin D (n=28) and then repeated the fully adjusted models for mean and maximum CCA-IMT. Last, because fruit also contains many phytochemicals thought to benefit cardiovascular health,[45] we explored the relationship of total fruit intake (per serving, 150 g/d) with CCA-IMT (mean and maximum) and carotid plaque severity using the 3 models of adjustment previously described plus an additional model further adjusting for total vegetable intake (per 75 g/d).

Results

Characteristics of Study Population

Participant demographics, medication use, and biochemical analyses of all 968 study participants and by categories of vegetable servings are presented in Table 1. Generally, higher intakes of vegetables corresponded to higher intakes of other foods and nutrients. Mean (SD) vegetable intake was 199.9 (78.0) g/d, and mean (SD) vegetable servings was 2.7 (1.0) for all participants (Table 2). Proportional intakes of vegetable types (including intake of potatoes and other vegetables) are presented in Figure 2. Mean (SD) mean CCA-IMT was 0.778 (0.129) mm, and mean (SD) maximum CCA-IMT was 0.922 (0.152) mm. More advanced carotid stenosis (≥25%) was present in 120 of 968 participants (12.4%), and less advanced carotid stenosis (<25%) was present in 848 of 968 participants (87.6%).

Common Carotid Artery Intima-Media Thickness

Total vegetable intake

In linear regression, for all models of adjustment, total vegetable intake was inversely associated with mean CCA-IMT and maximum CCA-IMT (Table 3). For each serving (75 g/d) higher in vegetables, there was an associated 0.011 mm (1.4%) lower mean CCA-IMT (*P*=0.014) and 0.016 mm (1.7%) lower maximum CCA-IMT (*P*=0.002) after adjusting for lifestyle and cardiovascular risk factors (Table 3). Similarly, participants consuming ≥3 servings of vegetables each day had ≈0.036 mm (4.6%) lower mean CCA-IMT and 0.047 mm (5.0%) lower maximum CCA-IMT compared with participants consuming <2 servings of vegetables (Table 3).

Vegetable types

In linear regression, for all models of adjustment, intake of cruciferous vegetables was inversely associated with mean CCA-IMT and maximum CCA-IMT (Table 4). This relationship remained significant after further adjustment for noncruciferous vegetable intakes. Legume intake was not associated with mean CCA-IMT. However, for maximum CCA-IMT, legume intake was inversely associated in unadjusted (*P*=0.023), and age and energy adjusted (*P*=0.044), models, but not the multivariable-adjusted model (*P*=0.085). Intakes of allium, yellow/orange/red, and leafy green vegetables were not significantly associated with mean or maximum CCA-IMT (Table 4).

Carotid Plaque Severity

Total vegetable intake and intake of vegetable types were not associated with carotid plaque severity (Table 5).

Sensitivity Analyses

In the separate linear regression analyses that additionally adjusted for individual dietary confounders, total fruit, fish, nuts, red meat, processed meat, fiber, magnesium, and monounsaturated fat did not change the interpretation of the association between total vegetable intake and CCA-IMT (Table 6). Adjustment for potassium and vegetable-derived nitrate, however, both attenuated the association between total vegetable intake and CCA-IMT. Adjustment for saturated fat intake attenuated the association between total vegetable intake and mean CCA-IMT, but not maximum CCA-IMT. Similarly, in the separate linear regression analyses that additionally adjusted for individual dietary confounders, total fruit, fish, nuts, fiber, magnesium, monounsaturated fat, and saturated fat did not change the interpretation of the association between intake of cruciferous vegetables and CCA-IMT (Table 6). Adjustment for potassium and vegetable-derived nitrate both attenuated the association between intake of cruciferous vegetables and maximum CCA-IMT, but not mean CCA-IMT. Exclusion of potatoes cooked without fat from total vegetable intake did not change the interpretation of the association between total vegetable intake and mean CCA-IMT (unstandardized ß=−0.018, SE=0.006, *P*=0.004) and maximum CCA-IMT (unstandardized ß=−0.025,

Table 1. Baseline Characteristics of All Study Participants and by Categories of Vegetable Servings*

Participant Demographics	All Participants (N=968)	<2 Servings (n=262)	2–<3 Servings (n=391)	≥3 Servings (n=315)	*P* Value
Age, y	75.0±2.6	75.0±2.6	74.9±2.6	74.9±2.6	0.896
BMI, kg/m^2	26.9±4.4	26.7±4.7	26.9±4.1	27.2±4.5	0.333
Body weight, kg	68.1±11.6	66.8±11.4	68.1±11.3	69.2±12.0	0.045
Physical activity, median (IQR), kJ/d	480.4 (169.3–856.2)	459.3 (0.0–862.8)	495.9 (188.1–890.7)	485.3 (179.4–805.0)	0.450
Alcohol intake, median (IQR), g/d	2.0 (0.3–10.0)	2.0 (0.3–9.1)	2.1 (0.4–10.6)	1.9 (0.3–9.9)	0.446
Smoking history, n (%)†	333 (34.6)	83 (31.8)	149 (38.3)	101 (32.3)	0.134
Socioeconomic status, n (%)‡					0.543
Top 10% most highly disadvantaged	35 (3.6)	8 (3.1)	14 (3.6)	13 (4.2)	
Highly disadvantaged	108 (11.3)	31 (11.9)	37 (9.5)	40 (12.9)	
Moderate-highly disadvantaged	153 (15.9)	43 (16.5)	61 (15.6)	49 (15.8)	
Low-moderately disadvantaged	149 (15.5)	44 (16.9)	55 (14.1)	50 (16.1)	
Low disadvantaged	205 (21.4)	51 (19.6)	81 (20.8)	73 (23.5)	
Top 10% least disadvantaged	310 (32.3)	83 (31.9)	142 (36.4)	85 (27.4)	
CAIFOS supplementation group, n (%)					0.045
Calcium	481 (49.7)	111 (42.4)	196 (50.1)	174 (55.2)	
Calcium plus vitamin D	28 (2.9)	9 (3.4)	12 (3.1)	7 (2.2)	
Placebo	459 (47.4)	142 (54.2)	183 (46.8)	134 (42.5)	
Medication use, n (%)					
Antihypertensive agents	389 (40.2)	103 (39.3)	150 (38.4)	136 (43.2)	0.408
Statin therapy	147 (15.2)	41 (15.6)	57 (14.6)	49 (15.6)	0.910
Low-dose aspirin	142 (14.7)	50 (19.1)	56 (14.3)	36 (11.4)	0.034
Biochemical analyses					
CKD-EPI eGFR, mL/min per 1.73 m^2§	67.6±12.9	66.9±13.3	67.9±12.2	67.8±13.3	0.553
Total cholesterol, mmol/L‖	5.9±1.1	6.0±1.1	6.0±1.0	5.8±1.1	0.265
HDL-C, mmol/L‖	1.5±0.4	1.5±0.4	1.5±0.4	1.4±0.4	0.125
LDL-C, mmol/L¶	3.7±1.0	3.8±1.0	3.8±0.9	3.7±1.0	0.425
Triglycerides, mmol/L‖	1.5±0.7	1.5±0.7	1.5±0.7	1.6±0.7	0.511

P values are a comparison between groups using ANOVA, Kruskal-Wallis test, and χ^2 test, where appropriate. Values are presented as mean±SD unless otherwise stated. BMI indicates body mass index; CAIFOS, Calcium Intake Fracture Outcome Study; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol.
*Vegetable servings were calculated on the basis of the 2013 Australian Dietary Guidelines of a vegetable serving equal to 75 g/d.
†n=963.
‡n=960.
§n=875.
‖n=895.
¶n=888.

SE=0.007, *P*=0.001). Furthermore, exclusion of participants who had received 1.2 g calcium carbonate plus 1000 IU of vitamin D (n=28) did not change the interpretation of the association of total vegetable intake and intake of cruciferous vegetables with CCA-IMT (mean and maximum) (Table 7).

Total fruit intake (per 150 g/d) was not associated with mean CCA-IMT and carotid plaque severity in all 3 models of adjustment (*P*>0.05 for all). There was evidence for an association between total fruit intake (per 150 g/d) and maximum CCA-IMT, but this was only statistically significant in the unadjusted (unstandardized ß=−0.012, SE=0.006, *P*=0.034) and multivariable-adjusted (unstandardized ß=−0.013, SE=0.006, *P*=0.042) models. Total fruit intake (per 150 g/d) was not associated with maximum CCA-IMT in the age- and energy-adjusted model (unstandardized ß=−0.011, SE=0.006, *P*=0.072) and in the multivariable-adjusted model after further adjustment for total vegetable intake (per 75 g/d) (unstandardized ß=−0.009, SE=0.006, *P*=0.166).

Table 2. Dietary Intakes of All Study Participants and by Categories of Vegetable Servings*

Dietary Intakes	All Participants (N=968)	<2 Servings (n=262)	2–<3 Servings (n=391)	≥3 Servings (n=315)	*P* Value
Vegetable servings, g/d	2.7±1.0	1.5±0.4	2.5±0.3	3.8±0.7	
Vegetables, g/d	199.9±78.0	113.4±28.1	186.5±21.2	288.5±56.5	<0.001
Cruciferous vegetables, g/d	32.3±22.0	18.6±12.8	30.5±17.7	46.0±24.8	<0.001
Allium vegetables, median (IQR), g/d	6.3 (2.9–10.7)	3.4 (1.7–6.2)	6.1 (3.4–10.2)	9.8 (5.9–15.3)	<0.001
Yellow/orange/red vegetables, g/d	53.7±27.7	31.0±14.6	51.6±18.2	75.2±29.5	<0.001
Leafy green vegetables, g/d	18.9±12.0	13.0±9.2	19.4±10.7	23.3±13.6	<0.001
Legumes, g/d	27.4±18.5	17.6±10.3	26.0±14.8	37.2±22.6	<0.001
Energy, kJ/d	7157.9±2076.8	6192.8±1753.4	6987.7±1891.9	8171.9±2106.3	<0.001
Total fat, g/d	64.6±23.3	57.1±20.3	63.4±22.6	72.3±24.1	<0.001
Saturated fat, g/d	25.7±11.2	23.9±10.4	25.1±11.1	28.0±11.6	<0.001
Monounsaturated fat, g/d	22.5±8.6	19.2±7.1	22.2±8.3	25.6±9.0	<0.001
Polyunsaturated fat, g/d	10.7±4.7	9.1±4.3	10.6±4.3	12.1±5.1	<0.001
Omega 3 fatty acids, g/d	1.3±0.6	1.1±0.5	1.3±0.5	1.6±0.7	<0.001
Dietary cholesterol, mg/d	237.8±97.8	214.6±87.8	232.6±94.3	263.4±104.3	<0.001
Protein, g/d	79.4±25.8	66.0±19.4	77.5±23.9	93.0±26.2	<0.001
Carbohydrate, g/d	192.3±57.6	164.8±49.3	186.1±49.6	222.8±59.3	<0.001
Sugar, g/d	92.9±31.2	81.1±28.6	89.6±28.4	106.9±34.3	<0.001
Fiber, g/d	23.0±7.8	17.6±5.2	22.4±6.0	28.1±8.1	<0.001
Potassium, mg/d	2966.6±841.9	2358.2±599.3	2872.0±653.3	3590.1±802.7	<0.001
Magnesium, mg/d	300.5±92.2	246.0±68.1	293.9±78.6	353.9±96.2	<0.001
Beta carotene, μg/d	2786.4±1275.2	1699.6±585.4	2680.1±844.6	3822.2±1327.3	<0.001
Fruit intake, g/d	258.3±129.6	206.0±108.2	252.8±108.6	308.8±150.0	<0.001
Nuts, median (IQR), g/d	0.6 (0.2–2.8)	0.3 (0.2–2.0)	0.6 (0.2–2.2)	1.0 (0.3–4.5)	<0.001
Fish, median (IQR), g/d	19.2 (9.5–35.6)	15.1 (6.4–25.9)	18.5 (8.7–33.2)	25.2 (13.8–48.7)	<0.001
Red meat intake, median (IQR), g/d	42.5 (23.7–68.5)	31.0 (15.2–48.5)	42.4 (24.8–64.5)	58.0 (32.3–92.2)	<0.001
Processed meat intake, median (IQR), g/d	10.2 (4.8–20.6)	9.6 (4.3–18.5)	10.6 (4.9–21.3)	10.7 (5.2–21.4)	0.091

P values are a comparison between groups using ANOVA and Kruskal-Wallis test, where appropriate. Values are presented as mean±SD unless otherwise stated. Cruciferous vegetables included cabbage, brussels sprouts, cauliflower, and broccoli. Allium vegetables included onion, leek, and garlic. Yellow/orange/red vegetables included tomato, capsicum, beetroot, carrot, and pumpkin. Leafy green vegetables included lettuce and other salad greens, celery, silver beet, and spinach. Legumes included peas, greens beans, bean sprouts, alfalfa sprouts, baked beans, soy beans, soy bean curd and tofu, and other beans. IQR indicates interquartile range.
*Vegetable servings were calculated on the basis of the 2013 Australian Dietary Guidelines of a vegetable serving equal to 75 g/d.

Discussion

In this cohort of older adult women, we found that both total vegetable intake and intake of cruciferous vegetables were inversely associated with mean and maximum CCA-IMT. These associations were independent of lifestyle and cardiovascular risk factors as well as other dietary confounders.

We observed a difference of 0.05 mm in maximum CCA-IMT between high and low intakes of total vegetables. This is likely to be clinically significant because a 0.1-mm decrease in carotid IMT is associated with a 10% to 18% decrease in risk of myocardial infarction and stroke.[5] The results of our study can be supported by a randomized controlled trial reporting a slight regression in CCA-IMT with dietary changes, which included an increased intake of fruit and vegetables over a 12-month period.[46] However, in observational studies, no associations have been observed between intakes of vegetables alone and carotid IMT, and they suggest fruit intake may be more beneficial.[47,48] Fruit intake, however, did not influence the association between total vegetable intake and CCA-IMT in our study, and it was not itself an independent predictor. Individual adjustments for potassium and vegetable-derived nitrate intakes did, however, attenuate the association between total vegetable intake and CCA-IMT. This suggests that at least some of the benefit from total vegetable intake was mediated by these components, which are also likely to influence vascular health.[43,49–52]

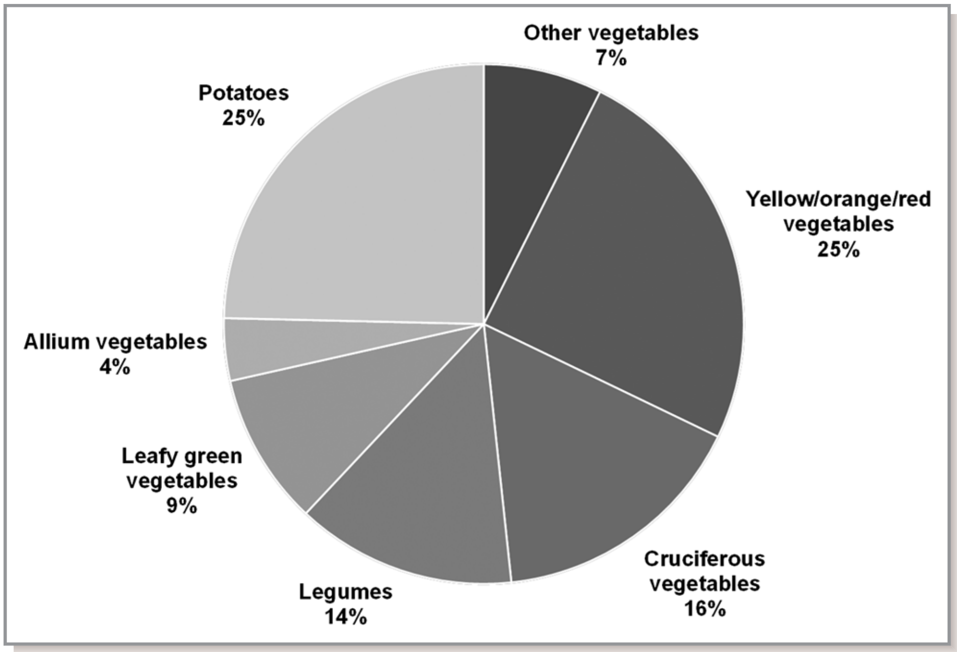

Figure 2. Percentage intake contribution of vegetable types from total vegetables (g/d) consumed.

There are many possible mechanisms to explain the relationship between higher vegetable intake and lower CCA-IMT. Vegetables have many important nutritive and nonnutritive constituents that may contribute to vascular health.[11] Phytochemicals have been postulated to have additional benefits beyond basic nutrients. These include polyphenols, which may play a role in scavenging free radicals that have the ability to oxidize low-density lipoprotein cholesterol infiltrated in the arterial wall.[53] Organosulfur compounds found abundantly in cruciferous vegetables may also play a role. Isothiocyanates are organosulfur compounds that have been extensively researched for their anticancer properties.[14,54–56] However, accumulating evidence suggests sulforaphane, a compound within the isothiocyanate group, may have beneficial effects on vascular damage via the blockade of oxidative stress and/or inhibition of advanced glycation end products.[57,58] There was strong evidence that intake of cruciferous vegetables was inversely associated with

Table 3. The Association of Vegetable Intake per Serving (75 g/d) and by Categories of Vegetable Servings With CCA-IMT

	All Participants*		Vegetable Serving Categories†			
Variables	B±SE (N=954)	*P* Value	<2 Servings (n=260)	2–<3 Servings (n=385)	≥3 Servings (n=309)	*P* Value
Mean CCA-IMT, mm						
Unadjusted	−0.013±0.004	0.002	0.797±0.008	0.780±0.007	0.760±0.007	0.003
Age and energy adjusted	−0.011±0.004	0.014	0.795±0.008	0.780±0.006	0.762±0.008	0.016
Multivariable adjusted‡	−0.011±0.005	0.014	0.788±0.013	0.770±0.012	0.752±0.013	0.014
Maximum CCA-IMT, mm						
Unadjusted	−0.017±0.005	<0.001	0.948±0.009	0.922±0.008	0.900±0.009	0.001
Age and energy adjusted	−0.016±0.005	0.002	0.946±0.010	0.922±0.008	0.901±0.009	0.004
Multivariable adjusted‡	−0.016±0.005	0.002	0.937±0.015	0.910±0.014	0.890±0.016	0.004

CCA-IMT indicates common carotid artery intima-media thickness.
*Results are analyzed by linear regression and are presented as unstandardized B and SE per serving (75 g/d).
†Results are analyzed by linear regression and are presented as estimated mean and SE.
‡Multivariable-adjusted model included age, body mass index, physical activity, alcohol intake, smoking history, socioeconomic status, the CAIFOS (Calcium Intake Fracture Outcome Study) supplementation group, antihypertensive agents, statin therapy, low-dose aspirin, Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate, and energy intake.

Table 4. The Association of Vegetable Types With CCA-IMT*

Variable	Mean CCA-IMT, mm		Maximum CCA-IMT, mm	
	B±SE (N=954)	*P* Value	B±SE (N=954)	*P* Value
Cruciferous vegetables, per 10 g/d				
Unadjusted	−0.006±0.002	0.002	−0.007±0.002	0.002
Age and energy adjusted	−0.006±0.002	0.003	−0.006±0.002	0.003
Multivariable adjusted†	−0.006±0.002	0.004	−0.007±0.002	0.005
Multivariable adjusted plus other vegetables	−0.005±0.002	0.011	−0.006±0.002	0.018
Allium vegetables, per 5 g/d				
Unadjusted	−0.001±0.003	0.679	−0.002±0.004	0.612
Age and energy adjusted	−0.001±0.003	0.680	0.001±0.004	0.793
Multivariable adjusted	0.001±0.004	0.847	0.000±0.004	0.970
Multivariable adjusted plus other vegetables	0.004±0.004	0.323	0.004±0.004	0.353
Yellow/orange/red vegetables, per 10 g/d				
Unadjusted	−0.002±0.002	0.142	−0.003±0.002	0.069
Age and energy adjusted	−0.002±0.002	0.334	−0.003±0.002	0.169
Multivariable adjusted	−0.002±0.002	0.268	−0.003±0.002	0.133
Multivariable adjusted plus other vegetables	0.000±0.002	0.879	−0.001±0.002	0.724
Leafy green vegetables, per 10 g/d				
Unadjusted	−0.005±0.003	0.175	−0.006±0.004	0.115
Age and energy adjusted	−0.004±0.003	0.228	−0.006±0.004	0.150
Multivariable adjusted	−0.005±0.004	0.190	−0.007±0.004	0.125
Multivariable adjusted plus other vegetables	−0.003±0.004	0.342	−0.005±0.004	0.277
Legumes, per 10 g/d				
Unadjusted	−0.004±0.002	0.083	−0.006±0.003	0.023
Age and energy adjusted	−0.003±0.002	0.152	−0.005±0.003	0.044
Multivariable adjusted	−0.003±0.002	0.234	−0.005±0.003	0.085
Multivariable adjusted plus other vegetables	−0.002±0.002	0.483	−0.003±0.003	0.255

CCA-IMT indicates common carotid artery intima-media thickness.
*Results are analyzed by linear regression and are presented as unstandardized B and SE.
†Multivariable-adjusted model included age, body mass index, physical activity, alcohol intake, smoking history, socioeconomic status, the CAIFOS (Calcium Intake Fracture Outcome Study) supplementation group, antihypertensive agents, statin therapy, low-dose aspirin, Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate, and energy intake.

mean CCA-IMT in this cohort, even after further adjustment for noncruciferous vegetables and other food and nutrients thought to be associated with cardiovascular health.

Focal carotid plaque severity was not associated with vegetable intake in this cohort of older adult women. Although CCA-IMT and carotid plaque are both intercorrelated, they may reflect different biological aspects of atherogenesis and are associated with different clinical vascular outcomes.[59] Carotid plaques are strongly related to hyperlipidemia and myocardial infarction, whereas CCA-IMT is more related to hypertension and ischemic stroke.[59] This may be because of focal plaque size being dependent on the influx of lipids into the plaque, whereas CCA-IMT captures both the atherosclerotic process as well as the nonatherosclerotic process, such as the compensatory thickening of the carotid wall as a response to ageing and hypertension.[60]

There are several strengths to this observational study. Study participants were representative of older adult women from the Australian population, with similar intakes of vegetable servings.[61] Furthermore, our study used 6 repeated measurements for both mean and maximum CCA-IMT and was shown to be highly reproducible, thereby reducing the likelihood of measurement error in this variable. However, since 2001, when the carotid ultrasounds were undertaken in the CAIFOS, sonographic characteristic evaluations have advanced (eg, surface irregularity, ulceration, and echogenicity). These sonographic characteristics along with resistive

Table 5. The Association of Total Vegetable Intake (per Serving, 75 g/d) and Intake of Vegetable Types With Carotid Plaque Severity*

Variable	All Participants	
	OR (95% CI) (N=968)	*P* Value
Total vegetables, per 75 g/d		
Unadjusted	1.01 (0.84–1.21)	0.916
Age and energy adjusted	1.02 (0.83–1.24)	0.866
Multivariable adjusted†	1.03 (0.82–1.28)	0.814
Cruciferous vegetables, per 10 g/d		
Unadjusted	1.05 (0.96–1.14)	0.283
Age and energy adjusted	1.05 (0.96–1.14)	0.294
Multivariable adjusted	1.03 (0.93–1.13)	0.569
Multivariable adjusted plus other vegetables	1.03 (0.93–1.13)	0.571
Allium vegetables, per 5 g/d		
Unadjusted	0.92 (0.79–1.07)	0.294
Age and energy adjusted	0.92 (0.78–1.08)	0.323
Multivariable adjusted	0.91 (0.76–1.08)	0.261
Multivariable adjusted plus other vegetables	0.89 (0.74–1.06)	0.201
Yellow/orange/red vegetables, per 10 g/d		
Unadjusted	1.03 (0.96–1.11)	0.379
Age and energy adjusted	1.04 (0.96–1.11)	0.344
Multivariable adjusted	1.04 (0.97–1.13)	0.252
Multivariable adjusted plus other vegetables	1.06 (0.97–1.14)	0.186
Leafy green vegetables, per 10 g/d		
Unadjusted	0.92 (0.78–1.08)	0.299
Age and energy adjusted	0.92 (0.78–1.08)	0.299
Multivariable adjusted	0.91 (0.75–1.09)	0.306
Multivariable adjusted plus other vegetables	0.90 (0.74–1.08)	0.268
Legumes, per 10 g/d		
Unadjusted	0.94 (0.84–1.05)	0.278
Age and energy adjusted	0.94 (0.84–1.05)	0.267
Multivariable adjusted	0.95 (0.84–1.07)	0.417
Multivariable adjusted plus other vegetables	0.94 (0.83–1.07)	0.356

CI indicates confidence interval; and OR, odds ratio.
*Vegetable servings were calculated on the basis of the 2013 Australian Dietary Guidelines of a vegetable serving equal to 75 g/d. Vegetable types included cruciferous vegetables (cabbage, brussels sprouts, cauliflower, and broccoli), allium vegetables (onion, leek, and garlic), yellow/orange/red vegetables (tomato, capsicum, beetroot, carrot, and pumpkin), leafy green vegetables (lettuce and other salad greens, celery, silver beet, and spinach), and legumes (peas, greens beans, bean sprouts, alfalfa sprouts, baked beans, soy beans, soy bean curd and tofu, and other beans). Carotid plaque severity was measured in 2001 (N=968). Results were analyzed by logistic regression.
†Multivariable-adjusted model included age, body mass index, physical activity, alcohol intake, smoking history, socioeconomic status, the CAIFOS (Calcium Intake Fracture Outcome Study) supplementation group, antihypertensive agents, statin therapy, low-dose aspirin, Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate, and energy intake.

index were not available to be analyzed in this study. In addition, only the CCA was assessed for IMT and not the bifurcation and internal carotid arteries. Further studies are, therefore, recommended to replicate the results of this study with these advanced measures. Other limitations include the possible reduced generalizability of study findings because of

Table 6. Multivariable-Adjusted Linear Regression Analyses That Additionally Adjusted for Individual Dietary Confounders*

Variable	Mean CCA-IMT, mm (N=954)		Maximum CCA-IMT, mm (N=954)	
	B±SE	*P* Value	B±SE	*P* Value
Cruciferous vegetables				
Multivariable adjusted plus total fruit, g/d†	−0.005±0.002	0.009	−0.006±0.002	0.012
Multivariable adjusted plus fish, g/d	−0.005±0.002	0.009	−0.006±0.002	0.010
Multivariable adjusted plus nuts, g/d	−0.006±0.002	0.005	−0.006±0.002	0.006
Multivariable adjusted plus red meat, g/d	−0.006±0.002	0.005	−0.007±0.002	0.005
Multivariable adjusted plus processed meat, g/d	−0.002±0.002	0.006	−0.007±0.002	0.006
Multivariable adjusted plus fiber, g/d	−0.006±0.002	0.006	−0.007±0.002	0.008
Multivariable adjusted plus potassium, mg/d	−0.004±0.002	0.035	−0.005±0.002	0.056
Multivariable adjusted plus magnesium, mg/d	−0.005±0.002	0.009	−0.006±0.002	0.013
Multivariable adjusted plus monounsaturated fat, g/d	−0.006±0.002	0.005	−0.006±0.002	0.007
Multivariable adjusted plus saturated fat, g/d	−0.005±0.002	0.019	−0.006±0.002	0.019
Multivariable adjusted plus vegetable-derived nitrate, mg/d	−0.005±0.002	0.039	−0.005±0.003	0.068
Total vegetables				
Multivariable adjusted plus total fruit, g/d	−0.010±0.005	0.035	−0.015±0.006	0.008
Multivariable adjusted plus fish, g/d	−0.010±0.005	0.022	−0.016±0.005	0.004
Multivariable adjusted plus nuts, g/d	−0.011±0.005	0.017	−0.016±0.005	0.003
Multivariable adjusted plus red meat, g/d	−0.012±0.005	0.008	−0.018±0.005	0.001
Multivariable adjusted plus processed meat, g/d	−0.011±0.005	0.018	−0.016±0.005	0.003
Multivariable adjusted plus fiber, g/d	−0.013±0.005	0.015	−0.018±0.006	0.003
Multivariable adjusted plus potassium, mg/d	−0.006±0.005	0.263	−0.010±0.006	0.138
Multivariable adjusted plus magnesium, mg/d	−0.010±0.005	0.034	−0.015±0.006	0.008
Multivariable adjusted plus monounsaturated fat, g/d	−0.011±0.005	0.017	−0.016±0.006	0.003
Multivariable adjusted plus saturated fat, g/d	−0.008±0.005	0.086	−0.013±0.006	0.017
Multivariable adjusted plus vegetable-derived nitrate, mg/d	−0.008±0.007	0.249	−0.012±0.008	0.114

CCA-IMT indicates common carotid artery intima-media thickness.

*Results are analyzed by linear regression and are presented as unstandardized B and SE.

†Multivariable-adjusted model included age, body mass index, physical activity, alcohol intake, smoking history, socioeconomic status, the CAIFOS (Calcium Intake Fracture Outcome Study) supplementation group, antihypertensive agents, statin therapy, low-dose aspirin, Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate, and energy intake.

the study involving 1154 of the original 1500 women (77%) recruited at baseline, particularly because this study was done 3 years after recruitment for the primary randomized controlled trial. In addition, classification by 1 characteristic results in differences in other characteristics, such as food and nutrient intakes. For example, participants consuming the highest servings of vegetables compared with participants consuming the lowest servings of vegetables reported a 32% higher energy intake, as well as most other foods and nutrients. Only marginal weight differences were observed for participants consuming the highest servings of vegetables compared with participants consuming the lowest servings of vegetables, even though there was a 32% higher energy intake reported. This suggests either errors in reported food intakes or, more likely, higher energy use. Last, only 1 measure of food intake and 1 measure for subclinical atherosclerosis were available; thus, the study resembles a cross-sectional design more than a prospective design. The study was conducted in older women only and, therefore, results need to be replicated in men and younger cohorts.

In conclusion, we found that both total vegetable intake and intake of cruciferous vegetables were inversely associated with CCA-IMT. These associations were independent of lifestyle and atherosclerotic-related risk factors as well as other dietary confounders. Increasing vegetables within the diet with a focus on consuming cruciferous vegetables may protect against subclinical atherosclerosis in older adult women.

Table 7. The Association of Total Vegetable Intake (per Serving, 75 g/d) and Intake of Cruciferous Vegetables (per 10 g/d) With Mean and Maximum CCA-IMT After Excluding Participants Who Had Received 1.2 g Calcium Carbonate Plus 1000 IU of Vitamin D (n=28)*

Variable	All Participants	
	B±SE (N=926)	*P* Value
Mean CCA-IMT		
Total vegetable intake, per 75 g/d	−0.011±0.005	0.017
Cruciferous vegetable intake, per 10 g/d	−0.006±0.002	0.006
Maximum CCA-IMT		
Total vegetable intake, per 75 g/d	−0.017±0.006	0.003
Cruciferous vegetable intake, per 10 g/d	−0.007±0.002	0.007

Cruciferous vegetables included cabbage, brussels sprouts, cauliflower, and broccoli. CCA-IMT indicates common carotid artery intima-media thickness.
*Results are analyzed by linear regression and are presented as unstandardized B and SE. Multivariable-adjusted model included age, body mass index, physical activity, alcohol intake, smoking history, socioeconomic status, the CAIFOS (Calcium Intake Fracture Outcome Study) supplementation group, antihypertensive agents, statin therapy, low-dose aspirin, Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate, and energy intake.

Acknowledgments

We thank the staff at the Data Linkage Branch and Hospital Morbidity Data Collection for their work on providing the data for this study.

Sources of Funding

The Calcium Intake Fracture Outcome Study was funded by Healthway Western Australian Health Promotion Foundation and the National Health and Medical Research Council of Australia (grant numbers 254627, 303169, and 572604). The analysis was supported by the National Health and Medical Research Council (NHMRC) of Australia (grant 1084922). The salary of Hodgson was supported by an NHMRC Senior Research Fellowship and a Royal Perth Hospital Medical Research Foundation Fellowship. The salary of Lewis was supported by an NHMRC Career Development Fellowship. None of these funding agencies had any role in the conduct of the study; collection, management, analysis, or interpretation of the data; or the preparation, review, or approval of the article.

Disclosures

None.

References

1. Aune D, Giovannucci E, Boffetta P, Fadnes LT, Keum N, Norat T, Greenwood DC, Riboli E, Vatten LJ, Tonstad S. Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality: a systematic review and dose-response meta-analysis of prospective studies. *Int J Epidemiol*. 2017;46:1029–1056.
2. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med*. 2005;352:1685–1695.
3. Manduteanu I, Simionescu M. Inflammation in atherosclerosis: a cause or a result of vascular disorders? *J Cell Mol Med*. 2012;16:1978–1990.
4. Ebrahim S, Papacosta O, Whincup P, Wannamethee G, Walker M, Nicolaides AN, Dhanjil S, Griffin M, Belcaro G, Rumley A, Lowe GDO. Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women. *Stroke*. 1999;30:841–850.
5. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation*. 2007;115:459–467.
6. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, Csiba L, Desvarieux M, Ebrahim S, Hernandez Hernandez R, Jaff M, Kownator S, Naqvi T, Prati P, Rundek T, Sitzer M, Schminke U, Tardif JC, Taylor A, Vicaut E, Woo KS. Mannheim carotid intima-media thickness and plaque consensus (2004–2006–2011). *Cerebrovasc Dis*. 2012;34:290–296.
7. Murie-Fernandez M, Irimia P, Toledo E, Martínez-Vila E, Buil-Cosiales P, Serrano-Martínez M, Ruiz-Gutiérrez V, Ros E, Estruch R, Martínez-González MÁ. Carotid intima-media thickness changes with Mediterranean diet: a randomized trial (PREDIMED-Navarra). *Atherosclerosis*. 2011;219:158–162.
8. Yang S-Y, Li X-J, Zhang W, Liu C-Q, Zhang H-J, Lin J-R, Yan B, Yu Y-X, Shi X-L, Li C-D, Li W-H. Chinese lacto-vegetarian diet exerts favorable effects on metabolic parameters, intima-media thickness, and cardiovascular risks in healthy men. *Nutr Clin Pract*. 2012;27:392–398.
9. Sala-Vila A, Romero-Mamani E-S, Gilabert R, Núñez I, de la Torre R, Corella D, Ruiz-Gutiérrez V, López-Sabater M-C, Pintó X, Rekondo J, Martínez-González M-Á, Estruch R, Ros E. Changes in ultrasound-assessed carotid intima-media thickness and plaque with a Mediterranean diet: a substudy of the PREDIMED trial. *Arterioscler Thromb Vasc Biol*. 2014;34:439–445.
10. Petersen KS, Clifton PM, Keogh JB. The association between carotid intima media thickness and individual dietary components and patterns. *Nutr Metab Cardiovasc Dis*. 2014;24:495–502.
11. Liu RH. Health-promoting components of fruits and vegetables in the diet. *Adv Nutr*. 2013;4:384S–392S.
12. Voutilainen S, Nurmi T, Mursu J, Rissanen TH. Carotenoids and cardiovascular health. *Am J Clin Nutr*. 2006;83:1265–1271.
13. Quiñones M, Miguel M, Aleixandre A. Beneficial effects of polyphenols on cardiovascular disease. *Pharmacol Res*. 2013;68:125–131.
14. Vazquez-Prieto MA, Miatello RM. Organosulfur compounds and cardiovascular disease. *Mol Aspects Med*. 2010;31:540–545.
15. Weitzberg E, Lundberg JO. Novel aspects of dietary nitrate and human health. *Annu Rev Nutr*. 2013;33:129–159.
16. Ashor AW, Lara J, Siervo M. Medium-term effects of dietary nitrate supplementation on systolic and diastolic blood pressure in adults: a systematic review and meta-analysis. *J Hypertens*. 2017;35:1353–1359.
17. Siervo M, Lara J, Ogbonmwan I, Mathers JC. Inorganic nitrate and beetroot juice supplementation reduces blood pressure in adults: a systematic review and meta-analysis. *J Nutr*. 2013;143:818–826.
18. Blekkenhorst LC, Bondonno CP, Lewis JR, Devine A, Zhu K, Lim WH, Woodman RJ, Beilin LJ, Prince RL, Hodgson JM. Cruciferous and allium vegetable intakes are inversely associated with 15-year atherosclerotic vascular disease deaths in older adult women. *J Am Heart Assoc*. 2017;6:e006558. DOI: 10.1161/JAHA.117.006558.
19. PLSAW Consortium. Perth Longitudinal Study of Ageing Women. 2016. http://www.lsaw.com.au/site/login. Accessed March 7, 2018.
20. Prince RL, Devine A, Dhaliwal SS, Dick IM. Effects of calcium supplementation on clinical fracture and bone structure: results of a 5-year, double-blind, placebo-controlled trial in elderly women. *Arch Intern Med*. 2006;166:869–875.
21. Bruce DG, Devine A, Prince RL. Recreational physical activity levels in healthy older women: the importance of fear of falling. *J Am Geriatr Soc*. 2002;50:84–89.
22. Zhu K, Devine A, Dick IM, Wilson SG, Prince RL. Effects of calcium and vitamin D supplementation on hip bone mineral density and calcium-related analytes in elderly ambulatory Australian women: a five-year randomized controlled trial. *J Clin Endocrinol Metab*. 2008;93:743–749.
23. World Health Organization. *Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death, 9th Revision (ICD-9)*. Geneva: World Health Organization; 1977.
24. National Centre for Classification in Health. *The Australian Version of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)*. Sydney: National Centre for Classification in Health; 1996.

25. Britt H, Scahill S, Miller G. ICPC PLUS for community health? A feasibility study. *Health Inf Manag*. 1997;27:171–175.

26. Salonen JT, Salonen R. Ultrasound B-mode imaging in observational studies of atherosclerotic progression. *Circulation*. 1993;87:II56–II65.

27. Lewis JR, Zhu K, Thompson PL, Prince RL. The effects of 3 years of calcium supplementation on common carotid artery intimal medial thickness and carotid atherosclerosis in older women: an ancillary study of the CAIFOS randomized controlled trial. *J Bone Miner Res*. 2014;29:534–541.

28. Wilson PWF, Hoeg JM, D'Agostino RB, Silbershatz H, Belanger AM, Poehlmann H, O'Leary D, Wolf PA. Cumulative effects of high cholesterol levels, high blood pressure, and cigarette smoking on carotid stenosis. *N Engl J Med*. 1997;337:516–522.

29. Ireland P, Jolley D, Giles G, O'Dea K, Powles J, Rutishauser I, Wahlqvist ML, Williams J. Development of the Melbourne FFQ: a food frequency questionnaire for use in an Australian prospective study involving an ethnically diverse cohort. *Asia Pac J Clin Nutr*. 1994;3:19–31.

30. Hodge A, Patterson AJ, Brown WJ, Ireland P, Giles G. The Anti Cancer Council of Victoria FFQ: relative validity of nutrient intakes compared with weighed food records in young to middle-aged women in a study of iron supplementation. *Aust N Z J Public Health*. 2000;24:576–583.

31. Woods RK, Stoney RM, Ireland PD, Bailey MJ, Raven JM, Thien FCK, Walters EH, Abramson MJ. A valid food frequency questionnaire for measuring dietary fish intake. *Asia Pac J Clin Nutr*. 2002;11:56–61.

32. Lewis J, Milligan G, Hunt A. *NUTTAB 95 nutrient data table for use in Australia*. Canberra: Australian Government Publishing Service; 1995.

33. National Health and Medical Research Council. *Australian dietary guidelines*. Canberra: National Health and Medical Research Council; 2013.

34. Blekkenhorst LC, Hodgson JM, Lewis JR, Devine A, Woodman RJ, Lim WH, Wong G, Zhu K, Bondonno CP, Ward NC, Prince RL. Vegetable and fruit intake and fracture-related hospitalisations: a prospective study of older women. *Nutrients*. 2017;9:511.

35. McArdle WD, Katch FI, Katch VL. *Energy, Nutrition and Human Performance*. Philadelphia, PA: Lea & Febiger; 1991.

36. Pollock ML, Wilmore JH, Fox SM. *Health and Fitness Through Physical Activity*. New York, NY: Wiley; 1978.

37. Australian Bureau of Statistics. Socio-economic indexes for areas. Catalogue number 2039.0. Canberra: Australian Bureau of Statistics; 1998.

38. Lewis JR, Lim W, Dhaliwal SS, Zhu K, Lim EM, Thompson PL, Prince RL. Estimated glomerular filtration rate as an independent predictor of atherosclerotic vascular disease in older women. *BMC Nephrol*. 2012;13:1–7.

39. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.

40. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499–502.

41. Bondonno N, Lewis J, Prince R, Lim W, Wong G, Schousboe J, Woodman R, Kiel D, Bondonno C, Ward N, Croft K, Hodgson J. Fruit intake and abdominal aortic calcification in elderly women: a prospective cohort study. *Nutrients*. 2016;8:159.

42. Blekkenhorst LC, Prince RL, Hodgson JM, Lim WH, Zhu K, Devine A, Thompson PL, Lewis JR. Dietary saturated fat intake and atherosclerotic vascular disease mortality in elderly women: a prospective cohort study. *Am J Clin Nutr*. 2015;101:1263–1268.

43. Bondonno CP, Blekkenhorst LC, Prince RL, Ivey KL, Lewis JR, Devine A, Woodman RJ, Lundberg JO, Croft KD, Thompson PL, Hodgson JM. Association of vegetable nitrate intake with carotid atherosclerosis and ischemic cerebrovascular disease in older women. *Stroke*. 2017;48:1–6.

44. Lupoli R, Vaccaro A, Ambrosino P, Poggio P, Amato M, Di Minno MND. Impact of vitamin D deficiency on subclinical carotid atherosclerosis: a pooled analysis of cohort studies. *J Clin Endocrinol Metab*. 2017;102: 2146–2153.

45. Bondonno NP, Bondonno CP, Ward NC, Hodgson JM, Croft KD. The cardiovascular health benefits of apples: whole fruit vs. isolated compounds. *Trends Food Sci Technol*. 2017;69:243–256.

46. Petersen KS, Clifton PM, Blanch N, Keogh JB, Petersen KS, Clifton PM, Blanch N, Keogh JB. Effect of improving dietary quality on carotid intima media thickness in subjects with type 1 and type 2 diabetes: a 12-mo randomized controlled trial. *Am J Clin Nutr*. 2015;102:771–779.

47. Chan HT, Yiu KH, Wong CY, Li SW, Tam S, Tse HF. Increased dietary fruit intake was associated with lower burden of carotid atherosclerosis in Chinese patients with type 2 diabetes mellitus. *Diabet Med*. 2013;30:100–108.

48. Buil-Cosiales P, Irimia P, Ros E, Riverol M, Gilabert R, Martinez-Vila E, Nunez I, Diez-Espino J, Martinez-Gonzalez MA, Serrano-Martinez M. Dietary fibre intake is inversely associated with carotid intima-media thickness: a cross-sectional assessment in the PREDIMED study. *Eur J Clin Nutr*. 2009;63:1213–1219.

49. Whelton PK, He J, Cutler JA, Brancati FL, Appel LJ, Follmann D, Klag MJ. Effects of oral potassium on blood pressure: meta-analysis of randomized controlled clinical trials. *JAMA*. 1997;277:1624–1632.

50. D'Elia L, Barba G, Cappuccio FP, Strazzullo P. Potassium intake, stroke, and cardiovascular disease: a meta-analysis of prospective studies. *J Am Coll Cardiol*. 2011;57:1210–1219.

51. Aburto NJ, Hanson S, Gutierrez H, Hooper L, Elliott P, Cappuccio FP. Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. *Br Med J*. 2013;346:f1378.

52. D'Elia L, Iannotta C, Sabino P, Ippolito R. Potassium-rich diet and risk of stroke: updated meta-analysis. *Nutr Metab Cardiovasc Dis*. 2014;24:585–587.

53. Sánchez-Moreno C, Jiménez-Escrig A, Saura-Calixto F. Study of low-density lipoprotein oxidizability indexes to measure the antioxidant activity of dietary polyphenols. *Nutr Res*. 2000;20:941–953.

54. Wu QJ, Yang Y, Vogtmann E, Wang J, Han LH, Li HL, Xiang YB. Cruciferous vegetables intake and the risk of colorectal cancer: a meta-analysis of observational studies. *Ann Oncol*. 2013;24:1079–1087.

55. Liu X, Lv K. Cruciferous vegetables intake is inversely associated with risk of breast cancer: a meta-analysis. *Breast*. 2013;22:309–313.

56. Liu B, Mao Q, Cao M, Xie L. Cruciferous vegetables intake and risk of prostate cancer: a meta-analysis. *Int J Urol*. 2012;19:134–141.

57. Bai Y, Wang X, Zhao S, Ma C, Cui J, Zheng Y. Sulforaphane protects against cardiovascular disease via Nrf2 activation. *Oxid Med Cell Longev*. 2015;2015:407580.

58. Yamagishi S, Matsui T. Protective role of sulphoraphane against vascular complications in diabetes. *Pharm Biol*. 2016;54:2329–2339.

59. Johnsen SH, Mathiesen EB. Carotid plaque compared with intima-media thickness as a predictor of coronary and cerebrovascular disease. *Curr Cardiol Rep*. 2009;11:21–27.

60. Plichart M, Celermajer DS, Zureik M, Helmer C, Jouven X, Ritchie K, Tzourio C, Ducimetière P, Empana J-P. Carotid intima-media thickness in plaque-free site, carotid plaques and coronary heart disease risk prediction in older adults. *Atherosclerosis*. 2011;219:917–924.

61. Australian Bureau of Statistics. National Health Survey: first results, 2014–15. Canberra: Australian Bureau of Statistics; 2015.

Journal of the American Heart Association
OPEN ACCESS

Cruciferous and Total Vegetable Intakes Are Inversely Associated With Subclinical Atherosclerosis in Older Adult Women

Lauren C. Blekkenhorst, Catherine P. Bondonno, Joshua R. Lewis, Richard J. Woodman, Amanda Devine, Nicola P. Bondonno, Wai H. Lim, Kun Zhu, Lawrence J. Beilin, Peter L. Thompson, Richard L. Prince and Jonathan M. Hodgson

J Am Heart Assoc. 2018;7:e008391; originally published April 4, 2018;
doi: 10.1161/JAHA.117.008391
The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980