RESEARCH ARTICLE

Dietary Patterns Associated With Risk of Intracranial Atherosclerosis in Older Adults With Hypertension or Myocardial Infarction

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Neurology® 2025;105:e214147. doi:10.1212/WNL.0000000000214147

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Abstract

Background and Objectives

Intracranial atherosclerosis disease (ICAD) accounts for 30% of ischemic strokes, has the highest stroke recurrence rate, and is associated with accelerated cognitive decline. This study investigates associations between diet patterns and the risk of ICAD.

Method

Participants in a longitudinal clinical neuropathologic cohort study, with complete dietary, medical history, and neuropathology data, were included. Diet scores were computed (median interval to death = 5.9 [3.0–8.7] years). History of hypertension (HTN) and myocardial infarction (MI) were self-reported. Large vessel ICAD was evaluated at the circle of Willis, and severity of ICAD was assessed based on number of atherosclerotic plaques, extent of vessel involvement, and degree of vessel occlusion to create a 4-level grading system (0–3). All regression models were adjusted for age, sex, education, caloric intake, and APOE4.

Results

Of the 676 participants (mean age at death = 91.1 years, SD = 6.1, 71% women), 361 (53%) had mild, 142 (21%) had moderate, and 28 (4%) had severe ICAD. There was no direct relationship between diet and ICAD. The association between ICAD and MI (OR 1.38, 95% CI 0.95–2.00) was not significant. HTN (OR 1.598, 95% CI 1.15–2.18) was positively associated with ICAD. The association of diet with ICAD differed by history of MI (Mediterranean-DASH intervention for neurodegenerative delay [MIND] [p = 0.007], MedDiet [p = 0.006]). The association between ICAD and the MIND diet also differed by whether HTN was reported ($\beta = -0.212$, SE = 0.111, $p = 0.055$) as did the relationship between ICAD and the MedDiet ($\beta = -0.077$, SE = 0.035, $p = 0.029$). In stratified analysis, among individuals with preexisting MI (N = 130), those with a better diet had lower odds of ICAD (MedDiet: OR 0.88, 95% CI 0.81–0.96; MIND: OR 0.69, 95% CI 0.53–0.90).

Discussion

A direct relationship between diet and ICAD was not seen. Stratified analysis suggested that healthy diet may be of value for individuals with HTN or MI: In these high-risk individuals, a healthy dietary pattern is associated with lower odds of severe large vessel ICAD. In vivo studies of dietary habits and brain health, specifically in those at high vascular risk, are needed.

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Supplementary Material

Introduction

Intracranial atherosclerotic disease (ICAD) is highly prevalent in community-based cohorts.[1] It is well established that ICAD causes ischemic stroke, with ICAD implicated as the etiology in up to 30% of all ischemic stroke cases, and even more frequently in African and Asian populations.[2] Ischemic strokes because of ICAD have the highest recurrence rate of all stroke subtypes, with

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Glossary

FFQ = Food Frequency Questionnaire; **ICAD** = intracranial atherosclerotic disease; **LDL** = low-density lipoprotein; **MAP** = Memory and Aging Project; **MI** = myocardial infarction; **MIND** = Mediterranean-DASH intervention for neurodegenerative delay; **OR** = odd ratio; **TMAO** = trimethylamine N-oxide.

a 10%–24% annual risk of stroke recurrence, despite optimized medical treatment.[3,4] In addition to its sizable contribution to the global burden of stroke, ICAD has been associated with faster cognitive decline and higher risk of dementia, even in stroke-free individuals.[5,6] As such, identifying key modifiable risk factors for ICAD, preventing its development, and implementing interventions to slow its progression is important.

Although previous epidemiologic studies have shown that ICAD is more common in individuals with uncontrolled vascular risk factors,[7,8] there are relatively little data on the pathophysiology of ICAD compared with extracranial carotid artery atherosclerosis or coronary artery atherosclerosis. One modifiable risk factor that may affect ICAD is diet. The Mediterranean-DASH intervention for neurodegenerative delay (MIND) diet, which combines the Mediterranean diet (MedDiet) and dietary approaches to stop hypertension diet, targets foods associated cognitive decline and reduce dementia risk.[1,9,10] In a recent observational cohort study, the MIND diet was associated with fewer cardiovascular events, including stroke, assessed over a 10 year of follow-up period.[11] Furthermore, a recent case-control study found the highest alignment with the MIND diet associated with a 59% lower stroke risk.[12]

Other studies have found similar results regarding the benefits of a healthy diet in reducing cardiovascular disease in individuals with elevated vascular risk. In the Lyon Diet Heart Study, survivors of myocardial infarction (MI) adhering to a MedDiet experienced a 70% reduction in stroke and recurrent MI after 4 years, compared with those following a "prudent Western" diet.[13] This was more than twice the effect of simvastatin in the Scandinavian Simvastatin Survival study, which also studied survivors of MI.[14] The MedDiet was also found to be protective in preventing cardiovascular events, including stroke, in high-risk individuals in the PREDIMED study.[15]

Although the associations among diet, vascular risk factors, and cardiovascular events are well-established, the role of diet in the development of ICAD in older brains is less clear, and even less well-established in individuals with preexisting vascular risk factors, such as hypertension (HTN) or a history of MI. Most studies on ICAD have used neuroimaging, with fewer studies examining neuropathology.[16] This study investigates the associations between diet patterns (MIND diet and MedDiet) and ICAD in older individuals with preexisting vascular risk factors, specifically history of HTN and MI. To this end, we leveraged dietary assessments and postmortem neuropathology from older, deceased participants with autopsies in the Rush Memory and Aging Project (MAP) to examine the associations between diet and ICAD in high-risk individuals.

Methods

Study Participants

The Rush MAP is an ongoing, longitudinal, clinicopathologic cohort study of aging and dementia, which started in 1997 and enrolls women and men from more than 40 retirement communities and housing facilities in the metropolitan Chicago area.[17] Eligibility requires the absence of known dementia and agreement to annual clinical evaluations and brain donation at death. To date, the follow-up rate exceeds 90%, and the autopsy rate exceeds 80%.

Standard Protocol Approval, Registrations, and Patient Consents

All participants signed an informed consent and an Anatomical Gift Act for organ donation, and the study protocol was approved by an Institutional Review Board of Rush University Medical Center.

Inclusion Criteria

MAP participants with complete food frequency questionnaire (FFQ) data who were deceased, with complete neuropathologic evaluation were included in the analysis.

Dietary Assessment

In MAP, dietary intake assessments began in February 2004 and has continued annually thereafter using a validated >144-item semiquantitative FFQ, modified from Harvard questionnaire for use older adults; validity and reliability of this FFQ has been established.[18] For each food item, participants were asked to report the usual frequency of intake during the past year. For each food item in the FFQ, total calories and nutrient levels were based either on natural portion sizes (e.g., 1 apple) or according to age-specific and sex-specific portion sizes from national dietary surveys, as previously defined.[9] In this study, we examined average MIND and MedDiet scores calculated using all available repeated FFQs assessed until death.

MIND Diet Score

The MIND diet score comprises 15 dietary components, each of which is summed to produce a score ranging from 0 to 15, with a higher score reflecting higher concordance,[9] 10 brain-

healthy food groups (green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, fish, poultry, olive oil, and wine) and 5 unhealthy food groups (red meats, butter and stick margarine, cheese, pastries and sweets, and fried foods). Consumption of the recommended amount or greater of the healthy food items were scored as a "1," whereas consumption of unhealthy food items was reverse coded, so that the "1" was scored if the participant consumed less of the item and "0" if they consumed more.[9]

MedDiet Score

The MedDiet score, as described by Panagiotakos et al.,[19] was also computed. This score comprises 11 dietary components, using serving sizes based on the traditional Greek MedDiet as the reference. Each component is scored 0 to 5, and all are summed for a total score ranging from 0 to 55 (highest dietary concordance).[10]

ICAD Outcome

Methods for brain autopsy and pathologic evaluation for vascular pathology have been previously described.[20] Briefly, ICAD assessment was completed by visual inspection of the circle of Willis, including the basilar, posterior cerebral, middle cerebral, and anterior cerebral arteries and their proximal branches. Vessels were visually inspected to determine the number of plaques, extent of involvement of each artery by plaques, and the degree of stenosis on bisecting vessels.[21] A 4-level scale was created for analysis with 0 for no significant ICAD observed; 1 for mild ICAD with small amounts in up to several arteries (typically less than 25% vessel involvement) without significant occlusion; 2 for moderate ICAD in up to half of all visualized major arteries, with less than 50% occlusion of any single vessel; and 3 for severe ICAD in more than half of all visualized arteries and/or more than 75% occlusion of 1 or more vessels (eTable 1).

HTN and MI

History of HTN was defined based on self-report and medication review (eAppendix 1).[22] History of MI was determined by the physician on the basis of clinical history, using close questions (yes/no) for patient response items (eAppendix 1).[23]

Other Covariates

Covariates examined included sociodemographic (age at death, sex, years of formal education) and the presence of APOE4 genotyping (at least 1 allele), which may promote atherosclerotic plaque formation by disrupting lipid homeostasis in macrophages and smooth muscle cells.[24,25] Smoking (never smoked, former smoker, or current smoker) and years of formal education were reported at enrollment (eAppendix 1). History of diabetes was defined based on self-report and medication review (eAppendix 1).[22] History of stroke and heart failure was determined by the physician on the basis of a uniform structured neurologic examination and clinical history (eAppendix 1). We also considered low-density lipoprotein (LDL) levels in blood (collected at last visit proximate to death) as a covariate where high LDL was defined as >115 mg/dL. Arteriolosclerosis (small vessel disease) is determined based on histologic examination using hematoxylin and eosin–stained sections of the anterior basal ganglia and computed as none-mild vs moderate-severe.[21]

Statistical Analysis

Spearman correlation was used to examine the correlation of MedDiet and MIND diet. Next, for each dietary pattern, we used a logistic regression model to test the hypothesis that greater dietary scores, reflecting healthier dietary habits, were associated with lower odds of ICAD at death, after controlling for age at death (continuous, years), sex, education (continuous, years), caloric intake (continuous, kcal/d), and APOE4 status. In addition, we also used separate logistic regression models to test the hypothesis that history of HTN and MI were associated with ICAD, adjusted for age at death, sex and education.

Next, to examine the interaction between continuous diet scores and history of MI, we fitted separate logistic regression models with 4-level ICAD as the outcome and terms for the continuous diet score, history of HTN, and a multiplicative term of these 2 in our model adjusted for age at death, sex, education, caloric intake, and APOE4 status. Similar analyses were repeated for history of HTN. For Figure 1, we assessed the MIND diet and MedDiet association with mild, moderate, and severe ICAD using natural cubic splines among those with and without history of MI.

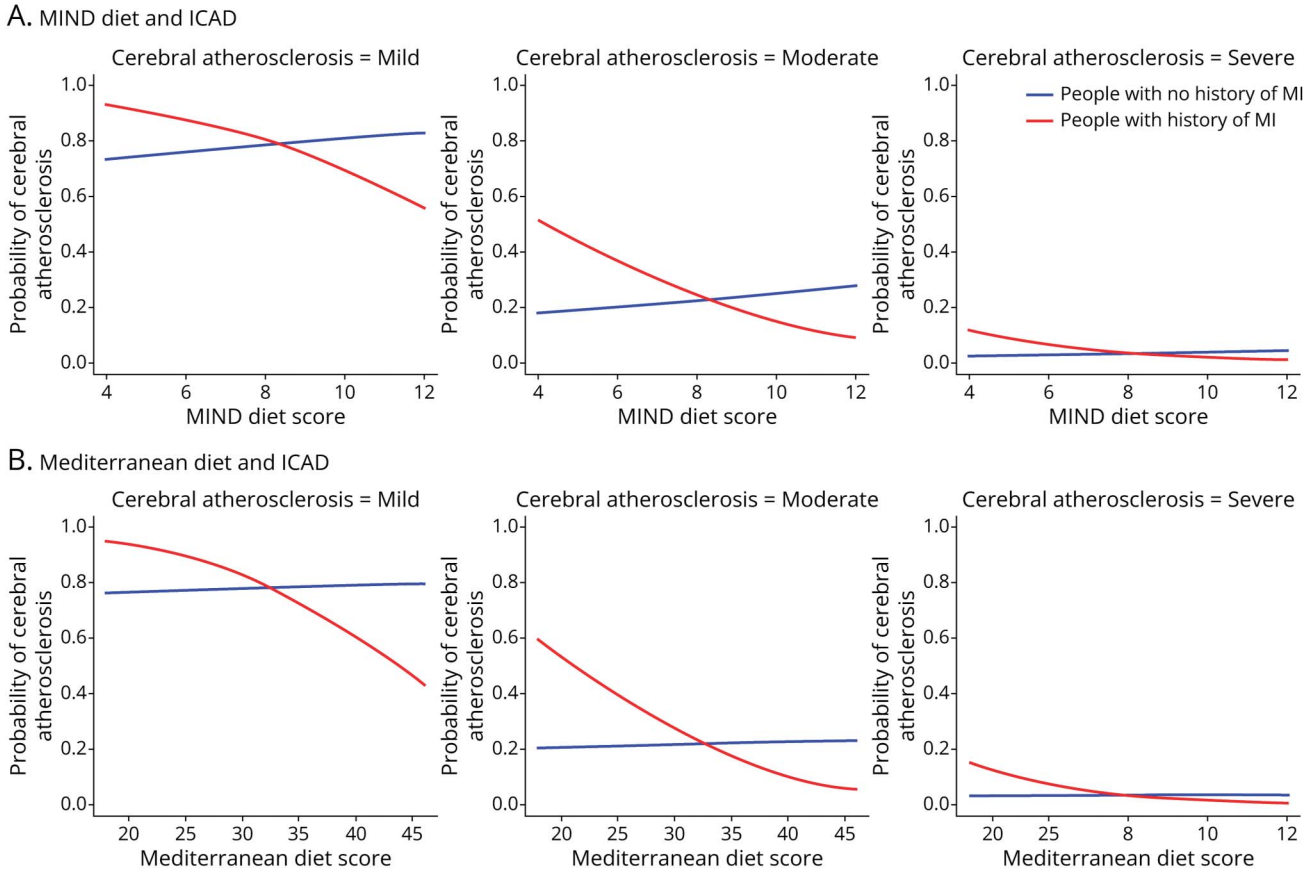
Finally, to provide a clinical context and a public health inference, we further dichotomized the cohort using the median diet score (7.5 for the MIND diet and 30 for the MedDiet) into a low diet score group, representing those with a less healthy diet, and a high diet score group, representing those with a healthier diet. This was done for both MIND and MedDiet scores. Using logistic regression models, we assessed the interaction of low/high diet and vascular risk (HTN and MI) for the association of these vascular risk factors with the 4-level ICAD outcome. When interactions were significant, we ran models for the association of diet with ICAD stratified by HTN or MI.

Sensitivity analyses were performed in models with the interaction terms by additional adjustment for potential confounders to assess the robustness of significant outcomes. We further adjusted for clinical vascular risk factors, including diabetes, stroke, heart failure, smoking, hyperlipidemia, and then arteriolosclerosis one at a time. All statistical analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC); statistical significance was identified as $p < 0.05$ on 2-tailed tests.

Data Availability

All data in these analyses (and descriptions of the studies and variables) can be requested through the Rush Alzheimer's Disease Center Research Resource Sharing Hub at radc.rush.edu.

Figure 1 Association of (A) MIND and (B) MedDiet With Mild, Moderate, and Severe ICAD Among Those With and Without a History of Heart Disease



ICAD = intracranial atherosclerotic disease; MedDiet = Mediterranean Diet; MIND = Mediterranean-DASH Intervention for Neurodegenerative Delay.

Results

Eligible Participants for Analysis

Of the 2,198 MAP participants who had completed the baseline clinical evaluation at the time of these analyses, we identified 2,042 individuals alive and active when the dietary substudy began in 2004. We excluded 162 participants without FFQ data during the follow-up (9 had withdrawn, 83 died, and 70 were Spanish speakers, had a clinical diagnosis of dementia, or declined to enroll in the dietary substudy), 486 with FFQ data unprocessed or incomplete, and 4 with FFQ data under quality check. Finally, we excluded 577 participants still alive, 111 decedents without complete brain autopsy to date, 26 decedents who did not yet have data on intracranial vascular neuropathology, and 1 participant missing HTN and MI history, leaving an analytic sample of 676 participants.

The analytic sample of 676 MAP participants had a mean age at death of 91.1 (SD = 6.1) years, and this was similar across the HTN and MI groups analyzed (Table 1). One hundred ninety-six (29%) participants were male, with higher percentages of men in the group without a history of HTN (39%) and in those with a history of MI (42%). Participants averaged 14.8 years (SD = 2.9) of education, independent of vascular risk factors. Mean MIND and MedDiet scores, assessed over a mean follow-up of 5.85 (SD = 3.92) years before death, were 7.4 (SD = 1.4) and 30.1 (SD = 4.5), respectively, and were highly correlated ($\rho = 0.69$, $p < 0.0001$). Of the 676 selected participants, 361 (53%) had mild, 142 (21%) had moderate, and 28 (4%) had severe ICAD.

Association of Diet, HTN, and MI With ICAD

Controlling for demographics, caloric intake, and APOE4 status, we did not find evidence that greater MIND diet scores (odd ratio [OR] 1.01; 95% CI 0.90–1.11; $p = 0.966$) and greater MedDiet scores (OR 0.98; 95% CI 0.94–1.01; $p = 0.235$) were associated with lower odds of ICAD (Table 2). In addition, controlling for demographics, history of MI was not associated with ICAD (OR 1.39; 95% CI 0.96–2.01; $p = 0.079$) (Table 2). However, history of HTN was associated with 55% higher odds of having ICAD at death (OR 1.55; 95% CI 1.13–2.13; $p = 0.006$), after controlling for demographics (Table 2).

Table 1 Demographic, Clinical, and Neuropathologic Characteristics by Presence or Absence of HTN and MI

Demographic, clinical, and neuropathologic characteristics	Overall (N = 676)	No HTN (n = 210)	History of HTN (n = 466)	No MI (n = 544)	History of MI (n = 132)
Demographics					
Age at death, y, mean (SD)	91.1 (6.1)	91 (6.0)	91.1 (6.2)	90.9 (6.1)	91.7 (5.9)
Male, n (%)	196 (29)	81 (39)	115 (25)	141 (26)	55 (42)
Education, y, mean (SD)	14.8 (2.9)	15 (2.9)	14.8 (2.8)	14.9 (2.8)	14.8 (3.1)
Race					
Non-Latino White	652 (96)	209 (99.5)	443 (95)	525 (96.5)	127 (96.2)
Non-Latino Black	13 (2)	1 (0.4)	12 (2.6)	11 (2.2)	2 (1.5)
Latino	9 (1)	0 (0)	9 (1.9)	6 (1.1)	3 (2.2)
Other	2 (0.3)	0 (0)	2 (0.3)	2 (0.4)	0 (0)
APOE4 carriers (at least 1 allele), n (%)[a]	142 (21)	47 (22)	95 (20)	123 (23)	19 (14)
Diet[b]					
MIND Diet score (possible score 0–15), mean (SD)	7.4 (1.4)	7.5 (1.4)	7.3 (1.4)	7.4 (1.4)	7.4 (1.3)
MedDiet score (possible score 0–50), mean (SD)	30.1 (4.5)	30.7 (4.6)	29.8 (4.4)	30.1 (4.6)	29.9 (4.2)
Total calories, kcal/d, mean (SD)	1,844.2 (528.7)	1,912.1 (552.2)	1,813.6.0 (515.5)	1,831.9 (523.9)	1,894.7 (547.2)
Vascular risk factors, n (%)[c]					
History of MI	132 (20)	38 (18)	94 (20)	—	—
History of HTN	466 (69)	—	—	372 (68)	94 (71)
History of diabetes	86 (13)	11 (5)	75 (16)	64 (12)	22 (17)
History of stroke[d]	133 (20)	32 (15)	101 (22)	89 (16)	44 (33)
History of HLD[e]	193 (29)	69 (33)	124 (27)	161 (30)	32 (24)
History of congestive heart failure[f]	94 (14)	20 (10)	74 (16)	58 (11)	36 (28)
History of smoking[g]	268 (40)	92 (44)	176 (38)	211 (39)	57 (43)
ICAD, n (%)[h]					
Absent	144 (21)	59 (28.10)	85 (18.24)	124 (22.79)	20 (15.15)
Mild	361 (53)	107 (50.95)	254 (54.51)	290 (53.31)	71 (53.79)
Moderate	142 (21)	33 (15.71)	109 (23.39)	107 (19.67)	35 (26.52)
Severe	28 (4)	11 (5.24)	17 (3.65)	23 (4.23)	5 (3.79)
Arteriolosclerosis[i]	191 (28)	59 (28)	132 (28)	152 (28)	39 (30)

Abbreviations: BP = blood pressure; HLD = hyperlipidemia; HTN = hypertension; ICAD = intracranial atherosclerosis disease; MedDiet = Mediterranean Diet; MI = myocardial infarction; MIND = Mediterranean-DASH Intervention for Neurodegenerative Delay.
Values are expressed as mean (SD), unless otherwise specified.
[a] Fourteen participants had missing data for ApoE4.
[b] Dietary scores and total calories represent mean values calculated over the entire follow-up until death.
[c] Vascular risk factors assessed at baseline and throughout follow-up.
[d] Five participants had missing data for stroke.
[e] Three participants had missing data for HLD.
[f] Eighty participants had missing data for CHF.
[g] Two participants had missing data for smoking.
[h] One participant was missing data for ICAD.
[i] Two participants had missing data for arteriosclerosis.

Table 2 Association of Diet Scores, HTN, and Myocardial Infarction With ICAD

Model	Model term	Odd ratio (95% CI)	*p* Value
Overall sample			
A[a]	MIND score	1.01 (0.90–1.11)	0.966
B[a]	MedDiet score	0.98 (0.94–1.01)	0.235
C[b]	History of MI	1.39 (0.96–2.01)	0.079
D[b]	History of HTN	1.55 (1.13–2.13)	0.006

Abbreviations: HTN = hypertension; ICAD = intracranial atherosclerosis disease; MedDiet = Mediterranean Diet; MI = myocardial infarction.
[a] Models were adjusted for age, sex, education, calories, and APOE4.
[b] Models were adjusted for age, sex, education.

Interaction Between Diet and Vascular Risk Factors for the Severity of ICAD

To examine whether the history of vascular risk factors modified the association between MIND diet and ICAD, regression models included an interaction term between MIND diet and the presence of history of MI or HTN in separate models (Table 3). The interaction term for MIND × MI was significant for ICAD (OR 0.69; 95% CI 0.53–0.91; $p = 0.007$), indicating that higher MIND diet scores were associated with a lower risk of ICAD in people with a history of MI compared with people without history of MI. Similarly, Med Diet × MI interaction term was also significant (Table 3).

In stratified analyses, the negative association of diet and ICAD was present only in those with history of MI (MIND: OR 0.77; 95% CI 0.59–1.01, $p = 0.053$; Med Diet: OR 0.88; 95% CI 0.81–0.97, $p = 0.010$, Table 3), indicating that healthy diet reduced the risk of ICAD in people with history of MI.

Next, we included an interaction between diet and history of HTN in the model of ICAD as an outcome (Table 4). The history of HTN and MedDiet diet interaction term in models of ICAD was significant, indicating that among people with history of HTN the inverse association between MedDiet diet and ICAD is stronger (Table 4). Although in stratified analysis, we did not find any association of either diet score with ICAD (Table 4).

In addition, we ran secondary analyses to examine whether the association of MI and HTN with ICAD varies by low (MIND <7.4, MedDiet <30) and high diet scores (MIND ≥7.4, MedDiet ≥30). The interaction term for MIND diet (MIND [low/high] × HTN: p for interaction = 0.49; MIND [low/high] × MI: p for interaction = 0.022) and MedDiet (MedDiet [low/high] × HTN: p for interaction = 0.055; MedDiet [low/high] × MI: p for interaction = 0.024) was assessed. In individuals with low diet scores, MI (MIND diet: OR 1.98, 95% CI 1.18–3.32; Med diet: OR 2.12, 95% CI 1.25–3.60) and HTN (MIND diet: OR 1.81, 95% CI 1.15–2.84; Med diet: OR 2.31, 95% CI 1.41–3.80) are associated with higher odds of ICAD. However, in individuals with high diet scores, no association was demonstrated: MI (MIND diet: OR 0.92, 95% CI 0.54–1.58; Med diet: OR 0.84, 95% CI 0.50–1.42) or HTN (MIND diet: OR 1.28, 95% CI 0.81–2.01; Med diet: OR 1.13, 95% CI 0.74–1.73).

Table 3 Association of MIND Diet and MedDiet With ICAD Among People With and Without History of MI

Model	Model term	Odd ratio (95% CI)	*p* Value
A	History of MI	20.73 (2.76–2,155.81)	0.003
	MIND score	1.07 (0.95–1.20)	0.233
	MIND × MI	0.69 (0.53–0.91)	0.007
B	History of MI	49.04 (3.60–667.29)	0.003
	MedDiet score	1.01 (0.97–1.05)	0.757
	MedDiet × MI	0.89 (0.81–0.97)	0.006
With MI history (n = 129)			
C	MIND score	0.77 (0.59–1.01)	0.053
D	MedDiet score	0.88 (0.81–0.97)	0.010
Without MI history (n = 527)			
E	MIND score	1.06 (0.94–1.19)	0.300
F	MedDiet score	1.01 (0.96–1.04)	0.700

Abbreviations: HTN = hypertension; ICAD = intracranial atherosclerosis disease; MedDiet = Mediterranean Diet; MI = myocardial infarction; MIND = Mediterranean-DASH Intervention for Neurodegenerative Delay.
All the logistic regression models adjusted for age at death, sex, education, total calories, APOE4 status. Models C–F are the stratified analyses with and without history of MI. There were missing covariates for 19 participants. One participant was missing data for ICAD.

Table 4 Association of MIND Diet and MedDiet on ICAD Among People With and Without History of HTN

Model	Model term	Odd ratio (95% CI)	*p* Value
A	History of HTN	7.9 (1.49–41.61)	0.015
	MIND score	1.16 (0.97–1.40)	0.199
	MIND × HTN	0.81 (0.65–1.01)	0.055
B	History of HTN	16.4 (1.95–137.85)	0.010
	MedDiet score	1.04 (0.98, 1.10)	0.199
	MedDiet × HTN	0.93 (0.86–0.99)	0.029
With HTN history (n = 448)			
C	MIND score	0.94 (0.83–1.07)	0.404
D	MedDiet score	0.96 (0.92–1.01)	0.126
Without HTN history (n = 208)			
E	MIND score	1.14 (0.95–1.37)	0.160
F	MedDiet score	1.03 (0.96–1.09)	0.400

Abbreviations: HTN = hypertension; ICAD = intracranial atherosclerosis disease; MedDiet = Mediterranean Diet; MI = myocardial infarction; MIND = Mediterranean-DASH Intervention for Neurodegenerative Delay.
All the logistic regression models adjusted for age at death, sex, education, total calories, APOE4 status. Models C–F are the stratified analyses with and without history of HTN. There were missing covariates for 19 participants. One participant was missing data for ICAD.

Sensitivity Analysis

We conducted 2 sensitivity analyses. First, we controlled for other vascular factors with the potential to affect associations of interaction between diet and MI or HTN with ICAD. Each of the following terms was added separately to the model with ICAD as the outcome: a history of HTN, diabetes, stroke, smoking, hyperlipidemia (as defined by blood LDL levels), or heart failure. The interaction results between both diets (MIND and MedDiet) and vascular risk factor (MI) to reduce the risk of ICAD were essentially unchanged ($p < 0.05$; data not shown). Finally, we controlled for arteriolosclerosis given that arteriosclerosis is strongly associated with ICAD. We found that the results were also unchanged ($p < 0.05$, data not shown).

Discussion

In this study of deceased community dwelling older adults, our primary analysis did not reveal an association between diet and ICAD neuropathology in the overall cohort. However, we found that within individuals with a history of HTN or MI, a healthy diet was associated with reduced risk of ICAD. In addition, we also found that among those with high diet scores, the association of MI or HTN with ICAD was attenuated. These findings suggest that a healthy diet may help preserve the vascular health of the brain for individuals with preexisting HTN or history of MI.

Previous studies have supported the association between diet and ICAD, although human studies of intracranial vascular neuropathology are lacking. In nonhuman primates, a high-fat and high-fructose diet was associated with the intracranial vessel infiltration of lipid-laden foam cells and the appearance of lipid droplet-filled smooth muscle cells, as well as increased vascular reactivity and vasoconstriction to stressors.[26] In the NOMAS MRI substudy, higher MedDiet scores were inversely related to ICAD, although this trend did not reach significance.[27] Metabolic syndrome, a common sequela of an unhealthy diet, has been associated with both extracranial and intracranial atherosclerotic disease on neuroimaging,[28] with ICAD worsening as the severity of the metabolic syndrome worsens.[29] A variety of previous studies including ours have found associations between a healthy diet, neuropathology, and functional outcomes, but the focus has been on Alzheimer pathology and other structural markers.[30-32]

To the best of our knowledge, this is the first study in humans evaluating the association of dietary patterns during on average 10 years of follow-up with intracranial vascular neuropathology at the time of death. Our analysis examining individuals with low and high diet scores found that diet may mitigating the risk of ICAD in the setting of existing vascular conditions, despite HTN and MI being known to be strongly associated with the development of ICAD. This may suggest that once diagnosed with HTN or MI, diet is of critical importance in protecting brain health through the prevention of ICAD.

The risk factors and mechanisms for ICAD are less well understood than those for systemic atherosclerosis.[33] However,

2 major components of ICAD formation are (1) atherosclerosis because of cholesterol deposition causing inflammation and (2) arterial stiffness resulting from endothelial dysfunction causing sclerosis.[33] Of the modifiable vascular risk factors, HTN may be the most important factor in the development of ICAD. In Asian and African populations, where the rates of ICAD are highest, the high prevalence of HTN is may partially explain the higher prevalence of ICAD compared with other populations.[7] Our finding that hypertensive individuals who consume a healthy diet have less ICAD than those who consume a less healthy diet offers a potential way to mitigate the risk of developing ICAD in high-risk populations.

Healthy diets, such as MIND and MedDiet, are primarily plant-based, high in fiber, essential nutrients, and antioxidants, and low in sugar and fat. A potential mechanistic link between diet and ICAD is the role of the gut microbiome and inflammation. The intestinal breakdown of dietary proteins, particularly those contained in red meat and egg yolks, creates metabolic products such as carnitine and phosphatidylcholine that cause atherosclerosis and increase cardiovascular risk in animal models.[34] The continued breakdown of these metabolites results in the production of trimethylamine N-oxide (TMAO). In a Cleveland Clinic study of individuals undergoing coronary angiograms, those with the highest quartile of plasma TMAO levels had a 2.5-fold increased risk of stroke, MI, or vascular death over a 3-year follow-up period.[35] As TMAO and other gut-derived uremic toxins are renally excreted, even mild renal impairment, which is common in individuals with HTN, can lead to elevated plasma levels.[34]

Another potential mechanism is the contribution of dietary fiber. The fiber content in healthy diets, such as the MIND and MedDiets, is higher than in a Western diet pattern. Fiber acts in multiple ways to improve metabolic health, including the prolongation of stomach emptying, lowering of postprandial blood glucose, and increase of bile excretion, which lowers total and LDL cholesterol. Lower total and LDL cholesterol levels have been associated with less atherosclerosis.[36] In addition, fiber intake causes stomach distention, which triggers the release of hormones that increase satiation, creating a feedback loop that improves metabolic health. Apo E4 status, best known for its role in Alzheimer dementia, has also been associated with a heightened risk of atherosclerosis.[37] The interplay between genetic risk, diet, vascular risk factors, and neuropathology (both vascular and degenerative) suggests a complex intracranial ecosystem that is just beginning to be fully understood. These hypothetical mechanisms must be further evaluated, particularly regarding intracranial vs extracranial atherosclerosis and potential variations related to the blood–brain barrier and other mediating factors.

The strengths of this study include a large number of autopsies, standardized neuropathologic measures, use of a validated FFQs administered annually, and structured clinical assessments from study enrollment until death. These measures reduce the selection bias resulting from loss to follow-up and the potential for measurement error. The limitations of this work include its observational study design, which precludes our ability to establish causal relationships. Self-reported history of hyperlipidemia was not available to include in these analyses and was defined as LDL >115 mg/dL, consistent with US POINTER study criteria for high-risk LDL. Another limitation of the study was self-reported history of MI, HTN, diabetes mellitus, and diet, which are subject to recall bias. However, these self-reported measures have been validated previously. Education level was used as a proxy for socioeconomic markers and could be predictive of access to care, such as income and insurance status. Analyses were not stratified by race because too few of the autopsied participants were non-White to provide robust statistical analyses. Given the heterogeneous prevalence of ICAD across demographic backgrounds, analyses by race would be valuable in studies with suitable participants and data. Given the limited availability of neuropathology, there were relatively few cases with absent ICAD, which may have affected the stability of point estimates in this analysis. The participants were mostly White, highly educated, healthy, non-Hispanic older individuals. Given these limitations, generalizations of these results to other population require caution. Future studies should explore potential mechanisms, particularly the role of inflammation and biomarkers, and the interplay between vascular neuropathology and other brain pathologies.

Diet was not associated with ICAD in the overall analytical sample from large group of autopsies from a community-based cohort of healthy older adults. However significant interaction between diet and history of HTN or MI warranted further investigation, and we found that in older adults with a history of HTN or MI, a healthy dietary pattern was associated with less severe ICAD. These data suggest that diet may be effective in maintaining vascular brain health in persons with a history of HTN or MI. In vivo studies of dietary habits and brain health are needed, specifically in those at high vascular risk.[38]

Acknowledgment

The authors thank the participants of the Rush Memory and Aging Project and key staff members. The authors also thank Traci Colvin, MPH, for coordination of the clinical data collection; Karen Skish, MS, for coordination of the pathologic data collection; and John Gibbons, MS, and Greg Klein, MS, for data management.

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Study Funding

The study was funded by NIH (R01AG17917, P30AG10161, R01AG15815, R01AG34374) and the Illinois Department of Public Health.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Previously published in medRxiv (doi:10.1101/2024.11.19.24317591). Received by *Neurology*® December 18, 2024. Accepted in final form August 6, 2025. Submitted and externally peer reviewed. The handling editor was Editor-in-Chief José Merino, MD, MPhil, FAAN.

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