Relative Intake of Macronutrients Impacts Risk of Mild Cognitive Impairment or dementia

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Abstract

High caloric intake has been associated with an increased risk of cognitive impairment. Total caloric intake is determined by the calories derived from macronutrients. The objective of the study was to investigate the association between percent of daily energy (calories) from macronutrients and incident mild cognitive impairment (MCI) or dementia. Participants were a population-based prospective cohort of elderly persons who were followed over a median 3.7 years (interquartile range, 2.5–3.9) of follow-up. At baseline and every 15 months, participants (median age, 79.5 years) were evaluated using the Clinical Dementia Rating scale, a neurological evaluation, and neuropsychological testing for a diagnosis of MCI, normal cognition, or dementia. Participants also completed a 128-item food-frequency questionnaire at baseline; total daily caloric and macronutrient intakes were calculated using an established database. The percent of total daily energy from protein (% protein), carbohydrate (% carbohydrate), and total fat (% fat) was computed. Among 937 subjects who were cognitively normal at baseline, 200 developed incident MCI or dementia. The risk of MCI or dementia (hazard ratio [HR], [95% confidence

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interval]) was elevated in subjects with high % carbohydrate (upper quartile: 1.89 [1.17–3.06]; P for trend=0.004), but was reduced in subjects with high % fat (upper quartile: 0.56 [0.34–0.91]; P for trend=0.03), and high % protein (upper quartile 0.79 [0.52 – 1.20]; P for trend=0.03) in the fully adjusted models. A dietary pattern with relatively high caloric intake from carbohydrates and low caloric intake from fat and proteins may increase the risk of MCI or dementia in elderly persons.

Keywords

Mild cognitive impairment; dementia; dietary proteins; dietary fats; dietary carbohydrates; caloric intake; energy intake; prospective studies; community-based

Introduction

Dietary patterns have been associated with late life cognitive function. High intakes of fruit, vegetables, a Mediterranean style diet, and several micronutrients (vitamins B, C, E) have been reported to have beneficial effects [1–4]. A high caloric intake has also been associated with an increased risk of cognitive impairment [5], and caloric restriction with reduced amyloid-β deposition [6–8]. The primary determinants of total caloric intake and the largest component of any diet consist of macronutrients: carbohydrates, fat, and protein. Yet, the role of macronutrient intake relative to total caloric intake on cognitive function in older persons has received little attention. Given the associations of macronutrients with glucose metabolism, neuronal integrity, and neuronal function [9–11], relative intake of macronutrients may have an etiologic role or may be a marker for late life cognitive impairment. We investigated the associations of percent of daily energy (calories) derived from carbohydrate, fat, and protein with risk of mild cognitive impairment (MCI) in a population-based cohort of elderly persons.

METHODS

Study Participants

The details of the study design have been published previously [12]. Briefly, we identified all Olmsted County, MN, residents aged 70–89 years on October 1, 2004, using the medical records-linkage system of the Rochester Epidemiology Project [13, 14]. From among the 9,953 subjects that were enumerated, 4,398 were eligible: 2,719 agreed to participate (61.8% response) by telephone (n=669) or via a face-to-face evaluation (in-person evaluation; n=2,050). We mailed the food frequency questionnaire to eligible in-person participants between the first and second evaluations; 681 who were not included at baseline were similar to 1,233 non-demented participants who were included regarding sex, BMI, and APOE ε4 allele status, but were older, had a higher frequency of hypertension, coronary heart disease, stroke, type 2 diabetes, depressive symptoms, were less likely to be married, and had lower education [2, 15]. Of the 1,233, 161 subjects had prevalent MCI at baseline, 26 had died, and 109 could not be contacted; 937 are included in this study (FIGURE 1).

Standard Protocol Approvals, Registrations, and Patient Consent

The study was approved by the institutional review boards of the Mayo Clinic and Olmsted Medical Center. Written informed consent was obtained prior to participation.

Measurements

Assessment of Cognitive Status—Each study participant underwent an interview by a nurse or study coordinator, a neurological evaluation by a physician, and cognitive testing.

The interview included questions about memory, date of birth, and years of education; the Clinical Dementia Rating (CDR) Scale [16] and the Functional Activities Questionnaire (FAQ) were administered to an informant [17]. The physician evaluation included the Short Test of Mental Status [18] and a complete neurological examination. The cognitive testing battery used nine tests to assess performance in four cognitive domains: memory, executive function, language, and visuospatial skills [12]. Each test score was converted to an age-adjusted Mayo's Older American Normative Studies scaled score (mean of 10, standard deviation of 3) [19]. Domain scores were computed by summing the age-adjusted and scaled test scores within a domain and rescaling the scores [12, 20].

Diagnostic Criteria—The domain scores were compared to the means (standard deviations) of scores generated from normal subjects from the Olmsted County population [19]. Cognitive impairment was considered possible if the domain score was 1.0 SD below the mean. The final decision about impairment in a cognitive domain was based on a consensus agreement among the examining physician, nurse, and neuropsychologist, taking into account education, prior occupation, and visual or hearing deficits [12, 20].

A diagnosis of MCI was made by consensus according to previously published criteria: cognitive concern by participant (from interview), informant (from CDR), nurse, or physician; impairment in one or more of the four cognitive domains from the cognitive testing battery; essentially normal functional activities (from CDR and FAQ); and absence of dementia [21]. A diagnosis of dementia was made according to the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* criteria [22]. Subjects were considered cognitively normal if they performed within the normal cognitive range and did not meet criteria for MCI or dementia [12, 20, 21].

Assessment of Dietary Macronutrient Intake—Usual dietary intakes in the previous twelve months were assessed from a self-administered modified Block 1995 Revision of the Health Habits and History Questionnaire [23] that was mailed to in-person participants [2, 15]. The questionnaire included 128 items (103 food items and 25 beverages). For each food item, participants 1) indicated their usual portion size consumed (small, medium, or large), with the medium size specified (e.g., medium serving=1 banana, 1 cup); and 2) how often they had consumed each food (never or <1/month, 1–3/month, 1/week, 2–4/week, 5–6/week, 1/day, 2–3/day, 4–5/day, 6+/day). We analyzed the data using the Food Processor SQL nutrition analysis software (version 10.0.0., ESHA Research, Salem, OR), under the direction of a registered dietician (H.M.O) [15, 24]. We calculated the total nutrient intake in grams per day (g/d) and total daily caloric intake (kcal/d).

Assessment of Covariates—We ascertained information on history of type 2 diabetes, hypertension, and coronary heart disease, from the participant's medical records [14]; a history of stroke was ascertained by the physician and verified in the medical record where possible [12]. We assessed depressive symptoms from an informant by interview using the Neuropsychiatric Inventory Questionnaire [24]. The frequency of moderate physical exercise in the year prior to the evaluation was assessed from self-report as: 1/month, 2–3/month, 1–2/week, 3–4/week, 5–6/week, and daily [25]. Body mass index (BMI) and apolipoprotein (*APOE*) ε4 genotyping were measured at baseline.

Longitudinal Follow-up

We evaluated participants at 15-month intervals using the same protocol that was used at baseline to determine cognitive function. Clinical and cognitive findings obtained from previous evaluations were not considered in making a diagnosis during follow-up. Subjects who declined an in-person evaluation at follow-up were invited to participate by a telephone

interview (partial participation) that included the Telephone Interview of Cognitive Status-modified (TICS-m) [26, 27], the Clinical Dementia Rating Scale [16] and the Neuropsychiatric Inventory Questionnaire [24].

Statistical Analyses

Subjects who were cognitively normal at baseline were considered at risk for incident MCI or dementia. The onset of event was defined by the midpoint between the last assessment as cognitively normal and the first-ever assessments as MCI or dementia. Subjects who refused to participate, could not be contacted, or died, were censored at their last evaluation. We computed years of follow-up as the time from the baseline evaluation to onset of MCI, onset of dementia, censoring, or date of last follow-up. Our analyses included only first ever MCI diagnoses, and did not consider subjects who reverted to normal after an initial diagnosis of MCI.

We calculated the energy-adjusted values of macronutrient intake (protein, carbohydrates, and fats) using the residual method as previously described [28]. We multiplied the daily intake of carbohydrate and protein (g/d) by 4, and fat intake by 9 to obtain the daily energy derived from each macronutrient. We computed the proportion of total daily energy derived from total carbohydrates (% carbohydrate), fat (% fat), and protein (% protein); from carbohydrate components (sugar, non-sugar carbohydrate, fiber); and fat components (polyunsaturated fatty acids [PUFA], monounsaturated fatty acids [MUFA], saturated fats [saturated fats], and trans-fatty acids), and ranked participants by quartiles of intake.

We examined the association of quartiles of % macronutrient intakes with incident MCI or dementia using proportional hazards models, with age as the time variable. In model 1, we adjusted for sex, number of years of education, propensity to participate at baseline using reciprocal probability weighting to adjust for potential non-participation bias at baseline [20, 29–31], and total caloric intake [32]. In a second model, we also adjusted for additional potential confounders including Apoe ε4 carrier status, type 2 diabetes, BMI, smoking status, depressive symptoms, moderate exercise (0 vs 1 time a month), stroke, marital status, alcohol intake, and longest held primary occupation (as a surrogate for socioeconomic status). In a separate model, we excluded subjects with a history of stroke because of the strong association of stroke with cognitive impairment. We could not adjust for ethnicity since the cohort was 99% white ethnicity. Since only 8 subjects developed dementia without an intervening diagnosis or MCI, our results are in regard to a composite endpoint of MCI or dementia.

RESULTS

TABLE 1 describes the characteristics of the 937 subjects who were cognitively normal at baseline. Median age was 79.5 years, 51% were male, 40% had 12 years of education, and 65% were married. A total of 200 subjects developed incident MCI or dementia over a median follow-up of 3.7 years (interquartile range, 2.5–3.9; 2871 person-years).

TABLE 2 describes the demographic, clinical characteristics and dietary intakes of subjects across quartiles of % carbohydrate at baseline. Subjects in the highest % carbohydrate quartile had a higher frequency of women and incident MCI or dementia compared to the lowest quartile; they were also less likely to be married and had a lower BMI. Of note, there were no significant trends with key known risk factors for MCI or dementia: frequency of APOE ε4 allele, type 2 diabetes, stroke, depressive symptoms, moderate exercise, and years of education. Intake (as g/day or % of energy) of sugar, other carbohydrates (non-sugar, non-fiber) and fiber increased across increasing % carbohydrate quartiles, but protein, fat,

and alcohol decreased. Total fruit intake increased across % carbohydrate quartiles however, vegetable intake was not different across quartiles.

TABLE 3 describes the association of % macronutrients with risk of MCI or dementia. The risk was elevated nearly 2-fold for the highest % carbohydrate quartile. In contrast, the risk was reduced at higher % fat and % protein quartiles. There was a trend toward increased risk with increasing % sugar. The significant trends persisted in the fully adjusted models that included adjusting for a history of stroke. The results did not change substantially even after exclusion of subjects with a history of stroke: HR (95% CI) for upper compared to lowest quartile were: 1.53 ([0.99–2.36]; p for trend = 0.08) for % carbohydrate; 0.66 ([0.42–1.03]; p for trend = 0.02) for % fat; 1.08 ([0.72–1.62]; p for trend = 0.15) for % protein; and 1.30 ([0.84–2.00]; p for trend = 0.14) for % sugar. In a multivariable model including carbohydrate, fat, and protein in the same model, carbohydrate remained significantly associated with MCI or dementia (upper vs. lowest quintile: 3.68 [1.61–8.38]; p for trend = 0.01); fat and protein no longer showed a significant trend (Table 4). There were no significant interactions of % carbohydrate, % fat, or % protein with age, sex, APOE ε4, or BMI.

Table 5 shows associations of intake of other carbohydrate, fiber, and fat components with MCI or dementia. The risk increased with increasing % other carbohydrate and fiber intake, and decreased with increasing % PUFA and % saturated fat, but the tests for trend were not significant.

DISCUSSION

In our population-based cohort of elderly persons, high % carbohydrate intake was associated with an increased risk of MCI. In contrast, high % fat and high % protein intake were associated with a reduced risk of MCI or dementia. These findings suggest that dietary patterns consisting of a high intake of energy derived from carbohydrates and a relatively low intake from fat and protein may have adverse implications for development of MCI. In contrast, an optimal balance in the proportions of daily calories derived from carbohydrate, fat, and protein, may maintain neuronal integrity and optimal cognitive function in the elderly.

A possible explanation for the association of carbohydrate intake with MCI is that elderly subjects with a high % carbohydrate intake may consume more foods with a high glycemic index. Indeed, subjects in our study with the highest % carbohydrate intake also had the highest intake of sugars and fruit (which are high in sugar content) but not vegetables, and the lowest intake of fat and protein. Glucose is a major source of energy for brain metabolism, and glucose administration typically enhances cognitive performance [33]. However, in elderly persons, a dietary pattern high in carbohydrate intake and in simple sugars may disrupt glucose and insulin metabolism [8, 34–38]. High insulin levels may be detrimental to cognitive function [38]. Persistence of the association of high % carbohydrate with MCI risk after simultaneous adjustment for fat and protein suggests that high intake of carbohydrate may be a key promoter of the increased risk, and relative intakes of protein and fat may also play a role.

High carbohydrate and sugar intake may adversely affect cognition through several mechanisms. Hyperglycemia and diabetes may contribute to increased formation of advanced glycation endproducts (AGE), upregulation of the soluble receptors for AGEs, and may generate oxidative stress which in turn, enhances AGE formation [39–41]. AGEs and oxidative stress have also been associated with greater cognitive decline and with AD through effects on amyloid and tau metabolism [39, 41].

The increased risk of MCI with lower intake of fats and proteins may involve non-energy related pathways [33]. Fat and protein intake may be required for the integrity of neuronal membranes and fats for the integrity of the myelin sheaths in the brain. Although we did not observe significant trends with increasing quartiles of % MUFA and % PUFA intake, the hazard ratios were reduced for higher intake. These unsaturated fatty acids, and in particular essential PUFAs, may maintain cognitive function through effects on structural, functional, and synaptic integrity of neurons [42–44], reduced amyloid-β levels [42], improved insulin sensitivity and glucose metabolism [45–47], decreased cardiovascular disease [48] and stroke [49]. High intake of fish, an important source of omega 3 PUFA, has been associated with a reduced risk of cognitive impairment in elderly persons [50] since fish is also an important source of vitamin D, the reduced risk of cognitive impairment in individuals with high fish intake may be due to the combined effects of omega 3 PUFA and vitamin D [51]. Low intake of protein may be associated with low intake of essential proteins that are required for synthesis of neurotransmitters in the brain. For example, tryptophan crosses the blood brain barrier and is a precursor for brain serotonin, an important neurotransmitter. Murine studies suggest that tryptophan transport across the blood brain barrier decreases with ageing [52]. If this is true in humans, reduced intake of proteins in the elderly may adversely impact neuronal function.

Other factors besides macronutrient intake may contribute to our findings. Subjects with the highest % carbohydrate intake had the lowest total caloric intake which is consistent with the low % fat intake, but is also consistent with low BMI in these subjects, and with previously reported decreased weight loss in the years preceding onset of dementia in elderly persons [53–55]. In addition, moderate alcohol intake has been reported to reduce risk of cognitive impairment [3] and may play a role on MCI risk in our cohort. The dietary patterns observed may be causal or alternately, may be a marker for preclinical disease and risk of cognitive impairment or dementia in elderly persons. These associations need to be examined in other longitudinal studies.

Our findings are consistent with findings from several studies. In one study, subjects with AD and vascular dementia had a high predilection for sugar and sweet foods [56]. Other investigators suggest that reducing caloric intake through carbohydrate restriction may reduce risk of cognitive impairment, AD [5, 57–62], and amyloid-β deposition and pathology [63]. In a study among non-diabetics, the highest cognitive performance was observed in subjects with the best glucose regulation [37, 64]. In the National Health and Nutrition Examination Survey, a dietary pattern with a high % fat was associated with better processing speed, learning, and memory; in contrast high % carbohydrate was associated with poor processing speed [65]. Other studies suggest that phosphatidylcholine, an essential PUFA, improved memory, learning, concentration, and the ability to memorize words in elderly subjects with memory decline [33], and that protein may enhance cognitive performance [65, 66] by improving glucose homeostasis [67]. Decreasing total calories and BMI with increasing % carbohydrate quartile may be markers for imminent cognitive impairment, and are consistent with decreasing weight prior to dementia onset in elderly persons [55].

Potential limitations of our findings include recall bias in reporting of dietary nutrients. This effect may be small in part because subjects were cognitively normal at the time the food frequency questionnaire was completed, and because our previously reported cross-sectional findings on diet and cognition [2, 15] are consistent with several other studies [1, 68–72]. Although the validity of food frequency questionnaires has been questioned, this concern may have greater bearing on studies regarding cancer risk [73]. Other experts suggest that use of the food frequency questionnaire is valid for ranking subjects according to food and nutrient intake as in the present study [74–76]. We could not estimate glycemic index (or

glycemic load) since this index is impacted by foods eaten together at a meal; the food frequency questionnaire only assessed usual eating habits in the previous 12 months. There is a potential for non-participation bias, but the higher frequency of vascular risk factors in non-participants suggests that the hazard ratios may be are biased toward a null association. The potential impact of reverse causality is unclear, but it is not possible to determine whether preclinical changes of AD, cerebrovascular disease, or other neurodegenerative pathology, contributed to dietary patterns at baseline. Finally, study participants were primarily of northern European ancestry and any generalizability to other ethnicities should be performed with caution.

Several strengths of our study should be noted. The study was specifically designed to investigate risk factors for MCI. The population-based design reduced selection bias and enhanced the external generalizability of the findings to the population [14]. The comprehensive evaluation of participants for MCI or dementia by 3 independent evaluators increased the internal validity of the findings. We categorized subjects on their usual macronutrient intake using data from a previously validated food frequency questionnaire [23], and assessed nutrient intakes using an established nutrition database. The prospective study design allowed us to estimate causal associations while taking into account potential confounding factors.

Acknowledgments

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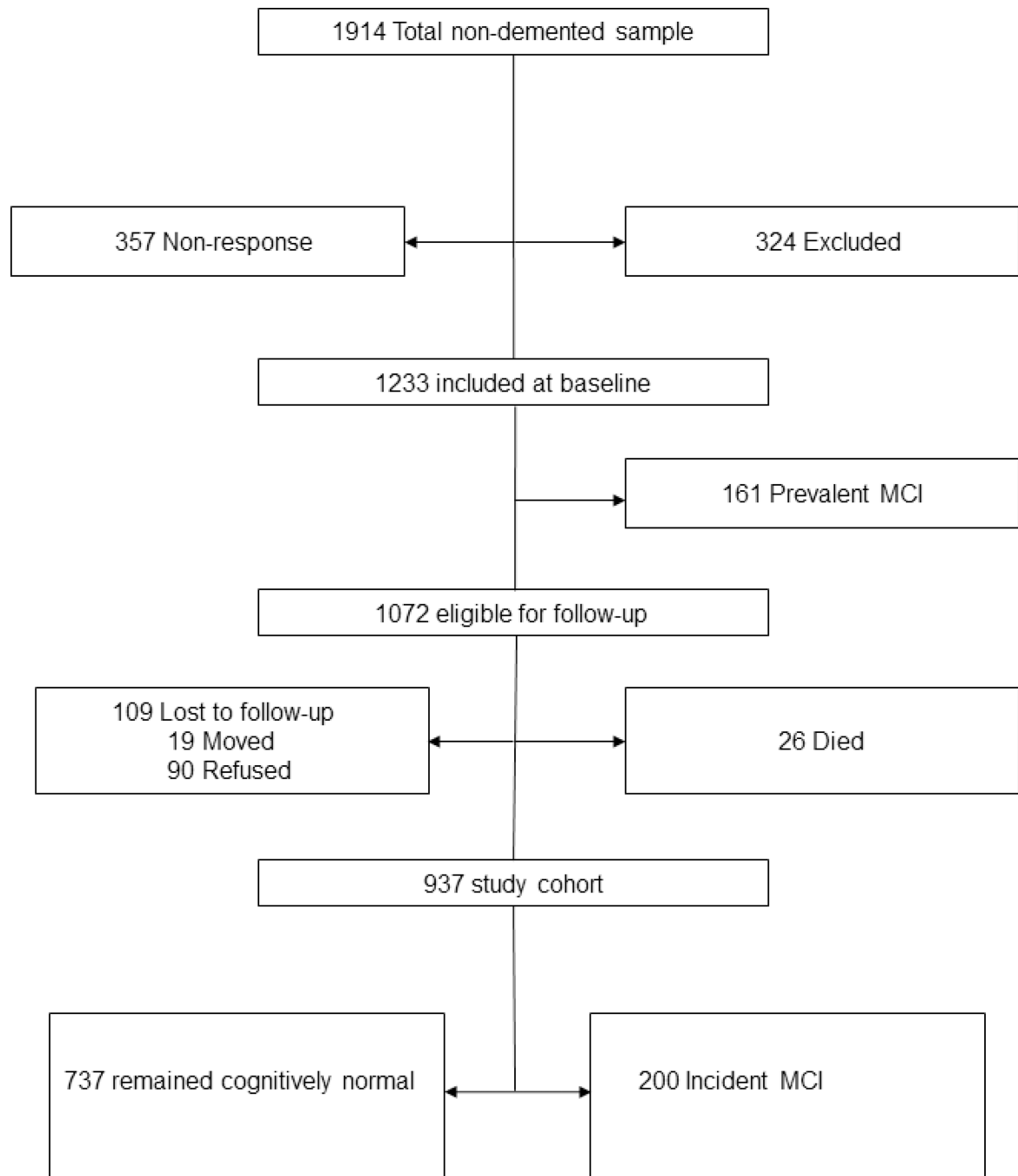
Figure 1.
Study Flow Chart. Excluded data: 268 had ≥10 missing responses on frequency of food consumption; 56 had extreme caloric intake (kcal/day: <800 in men, <600 in women or >6000 in men, >5000 in women).

Table 1

Demographic and Clinical Characteristics of Study Participants at Baseline

Variable	All N = 937
Age y, Med (Q1, Q3)	79.5 (75.3, 83.9)
Male Gender, n (%)	478 (51.0)
Education 12 y, n (%)	379 (40.4)
Married, n (%)	611 (65.2)
BMI 30, Kg/m^2 n (%)[a]	253 (27.7)
Type 2 diabetes, n (%)	149 (15.9)
Hypertension, n (%)	707 (75.5)
Coronary artery disease, n (%)	352 (37.6)
Stroke, n (%)	73 (7.8)
Depressive symptoms, n (%)[b]	91 (9.8)
APOE ε4, n (%)[c]	196 (21.5)
Moderate exercise, n (%)[d]	577 (64.3)
Caloric intake cal, med (Q1, Q3)	1791 (1352, 2351)
Total carbohydrate (g/day)	232 (172, 299)
Total protein (g/day)	78 (58, 103)
Total fat (g/day)	61 (43, 86)
Alcohol g/day, med (Q1, Q3)	0.4 (0.0, 6.0)
% Carbohydrate[e]	52 (47, 58)
% Fat[e]	31 (27, 35)
% Protein[e]	18 (16, 20)

Med (Q1, Q1), median (25th 75th) percentiles; BMI, body mass index; MCI, mild cognitive impairment, APOE, Apolipoprotein.

[a] 23 subjects with missing data, 4 with MCI and 19 without MCI.

[b] 12 subjects with missing data, 4 with MCI and 8 without MCI.

[c] 2 subjects without MCI with missing data, 23 subjects with ε2ε4 were excluded (7 with MCI and 16 without).

[d] 39 subjects with missing data, 16 with MCI group and 23 without.

[e] Percent of total daily energy from macronutrient.

Table 2

Characteristics of Subjects by % Carbohydrate Intake

Variable	Quartiles of % carbohydrate of total energy				P value
	Q1 <47% N = 234	Q2 47 – 52% N = 234	Q3 53 – 58% N = 235	Q4 >58% N = 234	
	N (%)				
Female	86 (36.8)	118 (50.4)	113 (48.1)	142 (60.7)	<0.001
Married[*]	176 (75.2)	145 (62.0)	153 (65.1)	137 (58.5)	0.001
APOE e4 carrier	50 (22.2)	39 (17.2)	51 (22.0)	56 (24.6)	0.27
Type 2 diabetes	47 (20.1)	29 (12.4)	41 (17.4)	32 (13.7)	0.09
Stroke	17 (7.3)	18 (7.7)	16 (6.8)	22 (9.4)	0.74
Depressive symptoms	30 (13.0)	22 (9.6)	21 (9.0)	18 (7.8)	0.27
Moderate exercise	140 (62.5)	138 (60.8)	156 (69.6)	143 (64.1)	0.23
Incident MCI	36 (15.4)	42 (17.9)	52 (22.1)	70 (29.9)	0.001
	Mean (SD)				
Age, yr,	78.8 (4.8)	80.1 (5.3)	79.9 (5.0)	80.9 (5.2)	<0.001
Education, yr	14.1 (3.1)	14.2 (3.0)	14.2 (3.0)	14.0 (2.7)	0.92
BMI, kg/m^2	28.8 (5.4)	27.8 (5.1)	27.4 (4.5)	26.8 (4.9)	<0.001
Total energy	2025 (841)	2004 (807)	1950 (850)	1770 (823)	0.004
Intake[†], g/day					
Total carbohydrate	189 (25)	221 (20)	245 (21)	273 (31)	<0.001
Sugar	78 (18)	99 (18)	112 (21)	129 (28)	<0.001
Other carbohydrates[‡]	74 (17)	80 (17)	88 (18)	91 (21)	<0.001
Fiber	18 (6)	22 (7)	24 (8)	29 (11)	<0.001
Protein	89 (17)	81 (14)	78 (14)	70 (15)	<0.001
Fat	75 (13)	65 (10)	59 (8)	49 (9)	<0.001
Alcohol	9 (13)	5 (10)	3 (6)	2 (5)	<0.001
Vegetables	217 (115)	235 (118)	224 (126)	233 (169)	0.43
Fruit	252 (126)	322 (151)	359 (190)	469 (265)	<0.001

Quartiles of % carbohydrate of total energy

Variable	Q1 <47% N = 234	Q2 47 – 52% N = 234	Q3 53 – 58% N = 235	Q4 >58% N = 234	P value
		N (%)			
Intake, % of energy					
% Total carbohydrate	41 (4)	50 (2)	55 (2)	63 (4)	<0.001
% Sugar	17 (4)	22 (4)	25 (4)	30 (6)	<0.001
% Other carbohydrate	16 (4)	18 (3)	20 (4)	21 (4)	<0.001
% Saturated fat	13 (3)	11 (2)	10 (2)	8 (2)	<0.001
% Protein	20 (4)	18 (3)	17 (3)	16 (4)	<0.001
% Total fat	37 (6)	33 (4)	30 (3)	25 (4)	<0.001
% MUFA	13 (3)	11 (2)	10 (1)	8 (2)	<0.001
% PUFA	6 (2)	6 (2)	5 (1)	5 (1)	<0.001
% Alcohol	4 (6)	2 (3)	1 (2)	1 (2)	<0.001

*
Married includes married or living with significant other

†
Estimates are age- and energy adjusted.

‡
Other carbohydrate consists of total carbohydrate – (total sugar + total fiber).

Table 3

Association of % Macronutrient (Carbohydrate, Fat, Protein, Sugar) With Incident MCI

Variable	Quartiles				P Value Trend [a]
	Q1	Q2	Q3	Q4	
% Total carbohydrate					
Cutpoint (%)	< 47	47 – 52	53 – 58	> 58	
Incident MCI, N (%)	36 (15)	42 (18)	52 (22)	70 (30)	
HR (95% CI) [b]	1.0 (referent)	0.99 (0.64–1.55)	1.21 (0.79–1.85)	1.80 (1.19–2.74)	0.007
HR (95% CI) [c]	1.0 (referent)	0.91 (0.55–1.50)	1.23 (0.76–1.99)	1.89 (1.17–3.06)	0.004
% Total Fat					
Cutpoint (%)	< 27	27 – 31	32 – 35	> 35	
Incident MCI, N (%)	63 (27)	58 (25)	38 (16)	41 (18)	
HR (95% CI) [b]	1.0 (referent)	0.81 (0.56–1.18)	0.50 (0.33–0.76)	0.58 (0.39–0.88)	0.005
HR (95% CI) [c]	1.0 (referent)	0.78 (0.52–1.19)	0.52 (0.32–0.84)	0.56 (0.34–0.91)	0.03
% Total Protein					
Cutpoint (%)	< 16	16 – 18	19 – 20	> 20	
Incident MCI, N (%)	63 (27)	42 (18)	41 (17)	54 (23)	
HR (95% CI) [b]	1.0 (referent)	0.70 (0.47–1.03)	0.70 (0.47–1.05)	1.02 (0.69–1.49)	0.09
HR (95% CI) [c]	1.0 (referent)	0.60 (0.39–0.91)	0.57 (0.36–0.89)	0.79 (0.52–1.20)	0.03
% Total Sugar					
Cutpoint (%)	< 19	19 – 23	24 – 27	> 27	
Incident MCI, N (%)	38 (16)	52 (22)	44 (19)	66 (28)	
HR (95% CI) [b]	1.0 (referent)	1.22 (0.81–1.85)	0.91 (0.59–1.42)	1.48 (0.98–2.24)	0.07
HR (95% CI) [c]	1.0 (referent)	1.18 (0.74–1.87)	0.84 (0.51–1.36)	1.51 (0.94–2.41)	0.05

Abbreviations: CI, confidence interval; HR, hazard ratio; MCI, mild cognitive impairment

[a] Test for trend across quartiles.

[b] Model 1, adjusted for sex, education (continuous), total daily energy (continuous), non-participation at baseline, and a single macronutrient.

[c] Model 2, adjusted for model 1 variables with additional adjustment for APOE e4, type 2 diabetes mellitus, depressive symptoms, body mass index (continuous), stroke, marital status, smoking status, alcohol (continuous), occupation (continuous), and frequency of moderate exercise.

Table 4

Simultaneous Assessment of Association of % Carbohydrate, %Fat, and % Protein With MCI or dementia

Variable	Q1	Q2	Q3	Q4	Q5	P Value Trend[a]
			Quintiles			
% Total carbohydrate						
Cutpoint (%)	<45	45–50	51–54	55–59	>59	
HR (95% CI)[b]	1.0 (referent)	1.63 (0.93–2.83)	1.47 (0.77–2.79)	1.96 (0.96–3.97)	3.68 (1.61–8.38)	0.01
HR (95% CI)[c]	1.0 (referent)	1.73 (0.93–3.23)	1.21 (0.57–2.57)	1.94 (0.81–4.65)	3.55 (1.24–10.18)	0.03
% Total Fat						
Cutpoint (%)	<26	26–30	31–33	34–36	>36	
HR (95% CI)[b]	1.0 (referent)	0.95 (0.61–1.48)	0.94 (0.54–1.63)	0.96 (0.50–1.84)	1.33 (0.64–2.77)	0.74
HR (95% CI)[c]	1.0 (referent)	1.04 (0.63–1.71)	0.92 (0.48–1.75)	0.94 (0.43–2.07)	1.24 (0.50–3.07)	0.87
% Total Protein						
Cutpoint (%)	<15	15–17	18–19	20–21	>21	
HR (95% CI)[b]	1.0 (referent)	0.94 (0.61–1.46)	0.88 (0.55–1.43)	1.13 (0.71–1.82)	1.50 (0.89–2.56)	0.29
HR (95% CI)[c]	1.0 (referent)	0.81 (0.50–1.31)	0.76 (0.44–1.33)	0.96 (0.55–1.65)	1.17 (0.61–2.24)	0.56

Abbreviations: CI, confidence interval; HR, hazard ratio; MCI, mild cognitive impairment

[a] Test for trend across quartiles.

[b] Model 1, adjusted for sex, education (continuous), total daily energy (continuous), and non-participation at baseline and all 3 variables in the same model.

[c] Model 2, adjusted for model 1 variables with additional adjustment for APOE e4, type 2 diabetes mellitus, depressive symptoms, body mass index (continuous), stroke, marital status, smoking status, alcohol (continuous), occupation (continuous), and frequency of moderate exercise.

Table 5

Association of % Other Carbohydrate, Fiber, and Fat Components with Incident MCI

Variable	Q1	Q2	Q3	Q4	P Value Trend [a]
% Other carbohydrates [b]					
Cutpoint (%)	< 16	16–19	20 – 21	> 21	
Incident MCI, N (%)	44 (19)	43 (18)	51 (22)	62 (27)	
HR (95% CI) [c]	1.0 (referent)	0.99 (0.65– 1.51)	1.24 (0.82– 1.86)	1.37 (0.93– 2.02)	0.26
HR (95% CI) [d]	1.0 (referent)	1.19 (0.75–1.90)	1.37 (0.87–2.17)	1.49 (0.97–2.30)	0.30
Dietary fiber g/d					
Cutpoint (%)	< 16	16 – 22	23 – 32	> 32	
Incident MCI, N (%)	37 (16)	51 (22)	58 (25)	54 (23)	
HR (95% CI) [b]	1.0 (referent)	1.51 (0.98–2.32)	1.66 (1.07–2.55)	1.69 (1.03–2.77)	0.11
HR (95% CI) [c]	1.0 (referent)	1.60 (1.00–2.57)	1.54 (0.94–2.53)	1.90 (1.09–3.31)	0.12
% Polyunsaturated fatty acids					
Cutpoint (%)	< 4.3	4 .3 – 5.2	5.3 – 6.1	> 6.1	
Incident MCI, N (%)	57 (24)	55 (24)	47 (20)	41 (18)	
HR (95% CI) [b]	1.0 referent)	1.09 (0.75–1.59)	0.85 (0.57–1.27)	0.73 (0.49–1.09)	0.22
HR (95% CI) [c]	1.0 (referent)	1.24 (0.81–1.89)	0.89 (0.58–1.38)	0.66 (0.42–1.05)	0.05
% Monounsaturated fatty acids					
Cutpoint (%)	< 8.9	9 – 10.5	10.6 – 12.0	> 12	
Incident MCI, N (%)	59 (25)	55 (24)	44 (19)	42 (18)	
HR (95% CI) [b]	1.0 (referent)	0.85 (0.58–1.25)	0.67 (0.45–1.01)	0.67 (0.44–1.03)	0.17
HR (95% CI) [c]	1.0 (referent)	0.88 (0.57–1.36)	0.69 (0.44–1.09)	0.78 (0.47–1.28)	0.45
% Saturated fats					
Cutpoint (%)	< 8.4	8.4 – 10.2	10.2 – 11.9	> 12	
Incident MCI, N (%)	64 (27)	47 (20)	52 (22)	37 (16)	
HR (95% CI) [b]	1.0 (referent)	0.72 (0.49–1.07)	0.67 (0.46–0.99)	0.56 (0.37–0.85)	0.04
HR (95% CI) [c]	1.0 (referent)	0.70 (0.45–1.09)	0.85 (0.55–1.32)	0.64 (0.39–1.05)	0.25
% Transfatty acids					

Variable	Quartiles				P Value Trend [a]
	Q1	Q2	Q3	Q4	
Cutpoint (%)	< 0.23	0.23 – 0.36	0.37 – 0.57	> 0.57	
Incident MCI, N (%)	53 (23)	49 (21)	50 (21)	48 (21)	
HR (95% CI) [b]	1.0 (referent)	0.75 (0.50–1.12)	0.76 (0.51–1.13)	0.67 (0.45–1.01)	0.25
HR (95% CI) [c]	1.0 (referent)	0.85 (0.55–1.33)	0.85 (0.54–1.33)	0.82 (0.52–1.30)	0.84

Abbreviations: CI, confidence interval; FA, fatty acids HR, fatty acids HR, hazard ratio; MCI, mild cognitive impairment; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

[a]Test for trend across quartiles.

[b]Non-sugar, non-fiber carbohydrates

[c]Model 1, adjusted for sex, education (continuous), total daily energy (continuous), non-participation at baseline, and a single macronutrient.

[d]Model 2, adjusted for model 1 variables and with additional adjustment for APOE e4, type 2 diabetes mellitus, depressive symptoms, body mass index (continuous), stroke, marital status, smoking status, alcohol (continuous), occupation (continuous), and frequency of moderate exercise.