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Caloric Intake, Aging, and Mild Cognitive Impairment: A Population-Based Study

Yonas E. Geda^{a,b,c,j,*}, Marion Ragossnig^d, Lewis A. Roberts^e, Rosebud O. Roberts^a, V. Shane Pankratz^f, Teresa J.H. Christianson^f, Michelle M. Mielke^a, James A. Levine^g, Bradley F. Boeve^h, Ondřej Sochorⁱ, Eric G. Tangalosⁱ, David S. Knopman^h, and Ronald C. Petersen^{a,h}

^aDivision of Epidemiology, Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA

^bDepartment of Psychiatry & Psychology, Mayo Clinic, Scottsdale, AZ, USA

^cDepartment of Neurology, Mayo Clinic, Scottsdale, AZ, USA

^dParacelsus Medizinische Privatuniversität, Salzburg, Austria

^eRice University, Houston, TX, USA

^fDivision of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA

^gDivision of Endocrinology and Metabolism, Mayo Clinic, Rochester, MN, USA

^hDepartment of Neurology, Mayo Clinic, Rochester, MN, USA

ⁱDivision of Primary Care Internal Medicine, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

^jInternational Clinical Research Center, Brno, Czech Republic

Abstract

In a population-based case-control study, we examined whether moderate and high caloric intakes are differentially associated with the odds of having mild cognitive impairment (MCI). The sample was derived from the Mayo Clinic Study of Aging in Olmsted County, Minnesota. Non-demented study participants aged 70–92 years (1,072 cognitively normal persons and 161 subjects with MCI) reported their caloric consumption within 1 year of the date of interview by completing a Food Frequency Questionnaire. An expert consensus panel classified each subject as either cognitively normal or having MCI based on published criteria. We conducted multivariable logistic regression analyses to compute odds ratios (OR) and 95% confidence intervals (95% CI) after adjusting for age, sex, education, depression, medical comorbidity, and body mass index. We also conducted stratified analyses by apolipoprotein E ε4 genotype status. Analyses were conducted in tertiles of caloric intake: 600 to <1,526 kcal per day (reference group); 1,526 to 2,143 kcal per day (moderate caloric intake group); and >2,143 kcal per day (high caloric intake group). In the primary analysis, there was no significant difference between the moderate caloric intake group and the reference group (OR 0.87, 95% CI 0.53–1.42, $p = 0.57$). However, high caloric intake was associated with a nearly two-fold increased odds of having MCI (OR 1.96, 95% CI 1.26–3.06, $p = 0.003$) as compared to the reference group. Therefore, high caloric intake was

*Correspondence to: Yonas E. Geda, Collaborative Research Building, Mayo Clinic, 13400 East Shea Blvd, Scottsdale, AZ 85259, USA; Telephone: 480-301-6120; Fax: 480-301-7017; geda.yonas@mayo.edu.

associated with MCI but not moderate caloric intake. This association is not necessarily a cause-effect relationship.

Keywords

aging; *APOE* ε4 genotype; caloric intake; mild cognitive impairment; population-based

INTRODUCTION

Mild cognitive impairment (MCI) is an intermediate stage between the cognitive changes of normal aging and dementia [1, 2]. Subjects with MCI constitute a high-risk group because they develop dementia at a rate of 10–15% per year compared with 1–2% per year in the general population [3]. In view of this, it is critical to identify risk factors for MCI.

While associations between specific diets and MCI were reported [4, 5], the focus of the current study is on total reported daily caloric intake regardless of the source of the energy. Investigators have reported that higher caloric intake is associated with a higher risk of Alzheimer's disease (AD) among apolipoprotein E (*APOE*) ε4 carriers [6]; however, little is known about the association of daily caloric intake with MCI [7]. Therefore, we examined whether caloric intake is associated with MCI in a case-control study derived from an ongoing population-based study of normal cognitive aging and MCI in Olmsted County, Minnesota.

METHODS

Setting

The details of the design and conduct of the Mayo Clinic Study of Aging were reported elsewhere [8]. Briefly, it is an on-going population-based study of normal aging and MCI in Olmsted County, Minnesota. Elderly persons aged 70–89 years on the prevalence date of October 1, 2004, were recruited by using a stratified random sampling from the target population of nearly 10,000 elderly individuals in Olmsted County, Minnesota. The sampling involved equal allocation of men and women in two age strata: 70–79- and 80–89-years-old. In the 70–79 years-old stratum, the intended sample was 500 men and 500 women; in the 80–89 years-old stratum, the intended sample was 550 men and 550 women. The actual sample for this study is described as follows. During the first follow-up phase of the study, which took place between 2006 and 2008, we administered a Food Frequency Questionnaire (FFQ) to collect data on caloric intake [5, 9]. The study sample consisted of 1,233 non-demented study participants who completed the FFQ. The Mayo Clinic Study of Aging cohort is followed every 15 months. At the time of completion of FFQ, neither the study participant nor the research personnel knew the case-control status of a participant. The study was approved by the institutional review boards of Mayo Clinic and Olmsted Medical Center.

Study design

A cross-sectional case-control study derived from the population-based cohort of the Mayo Clinic Study of Aging, involving 1,233 non-demented study participants: 161 subjects with MCI (cases) and 1,072 cognitively normal persons (controls).

Measurement of mild cognitive impairment (MCI)

Each participant in the Mayo Clinic Study of Aging underwent the following three face-to-face evaluations: 1) neurological evaluation by a physician. The evaluation included

administration of the Short Test of Mental Status [10], medical history review, and a complete neurological examination; 2) Risk factor ascertainment by a nurse or study coordinator. Additionally, the nurse or study coordinator administered Clinical Dementia Rating Scale [11] to the participant and to an informant; 3) Neuropsychological testing was administered by the psychometrist who was supervised by a neuropsychologist. The neuropsychologist also interpreted the psychometric data.

Neuropsychological testing was performed to assess four cognitive domains: 1) memory (Logical Memory-II [delayed recall] and Visual Reproduction-II [delayed recall] from the Wechsler Memory Scale-Revised, and delayed recall from the Auditory Verbal Learning Test [12–15]); 2) executive function (Trail Making Test B [16] and Digit Symbol Substitution from the Wechsler Adult Intelligent Scale-Revised); 3) language (Boston Naming Test [17] and category fluency [18]); and 4) visuospatial skills (Picture Completion and Block Design from the Wechsler Adult Intelligent Scale-Revised).

We considered as cases all participants who met the revised published criteria for MCI [2, 19]: 1) cognitive concern expressed by a physician, informant, participant, or nurse; 2) cognitive impairment in one or more domains (executive function, memory, language, or visuospatial); 3) normal functional activities; and 4) not demented. Subjects with MCI could have a Clinical Dementia Rating Scale score of 0 or 0.5; however, the final diagnosis of MCI was not based exclusively on the clinical dementia rating but rather on all available data. The diagnosis of normal cognition, MCI, or dementia was made by an expert consensus panel of physicians, psychologists, and nurses based on published criteria [8, 20, 21].

Measurement of caloric intake

We defined the exposure of interest to be daily caloric intake derived from the FFQ, a modified version of a previously validated instrument [5, 22]. The questionnaire included 103 food items, 25 beverages, cooking doneness for 7 meats, and use of 15 types of supplements; it focused on usual eating habits during the year prior to survey completion, including food eaten in a restaurant. 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. Using this database, we multiplied daily food consumption by 30 and weekly food consumption by 4 to determine monthly intake, and calculated the total nutrient intake (grams) and total caloric intake (kilocalories [kcal] per day).

Measurement of covariates

In addition to traditional confounders (age, sex, and education), we also included medical comorbidity, depression, and body mass index (BMI) as covariates. We also conducted stratified analyses by *APOE* $\epsilon 4$ allele status. We measured medical comorbidity by using the Charlson Index, a widely-used weighted index that takes into account the number and severity of diseases. Thus, for each unit increase in Charlson Index, there is a stepwise increase in the cumulative mortality attributable to the comorbid medical disease [23]. We measured depressive symptoms with the Beck Depression Inventory-II (BDI-II) [24]. We measured *APOE* genotype by using standard procedure [25]. A participant that has one (heterozygous) allele genotype or two (homozygous) allele genotypes of *APOE* $\epsilon 4$ is considered exposed or positive for *APOE* $\epsilon 4$.

Statistical analysis

Multi-variable logistic regression analyses were conducted to examine the strength of association between caloric intake and the odds of having MCI (primary analysis) by

computing odds ratios (OR) and 95% confidence intervals (95% CI). We arbitrarily created three groups and conducted analyses in tertiles of caloric intake: 600 to <1,526 kcals per day was defined as the reference group; 1,526 to 2,143 kcals per day (moderate caloric intake group), and >2,143 kcals per day (high caloric intake group). We compared the moderate caloric intake group with the reference group; similarly, we compared the high caloric intake group with the reference group in order to investigate whether daily moderate caloric intake and high caloric intake differ in their association with MCI. Additionally, we conducted secondary analyses wherein we examined the association between caloric intake and MCI subtypes (amnesic [aMCI] and non-amnesic [naMCI]). All the models were adjusted for age (continuous variable), sex, education (continuous variable), depressive symptoms (BDI-II score <13 versus ≥13), and BMI. We adjusted for medical comorbidity as measured by the Charlson Index as a continuous variable (range 0–33) [23]. The Charlson Index takes into consideration both the number and severity of diseases. Seventeen medical comorbidities are taken into account by the Charlson Index, including history of diabetes mellitus, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, kidney disease, and cancer. We also ran stratified analyses by *APOE* ε4 allele status. Statistical testing was done at the conventional two-tailed alpha level of 0.05. All analyses were performed by using SAS® (SAS Institute, Cary, NC).

RESULTS

Table 1 summarizes the demographic data. There were 1,233 non-demented study participants (161 subjects with MCI, and 1,072 cognitively normal persons). Seventeen subjects with dementia were excluded from the study. Out of the 161 subjects with MCI, the majority were classified with aMCI ($n = 113$), whereas 41 were classified with naMCI. We did not have adequate data to classify the remaining 7 subjects as either amnesic or non-amnesic.

Subjects with MCI were older, had higher frequencies of *APOE* ε4 allele, medical comorbidity, depression, and lower education than cognitively normal subjects, but there was no statistically significant difference between the two groups with regard to sex and BMI. Cognitively normal subjects had a higher frequency of obesity (defined as BMI >30 kg/m² per World Health Organization guidelines) [26].

Primary analysis (comparison of MCI [aMCI and naMCI] and controls)

Table 2 displays the data comparing the two groups as measured by OR (95% CI). There was no significant difference in OR between moderate caloric intake (1,526–2,143 kcal per day) and the reference group (OR 0.87, 95% CI 0.53–1.42, $p = 0.57$) whereas, high caloric intake (>2,143 kcals per day) nearly doubled the odds of having MCI (OR 1.96, 95% CI 1.26–3.06, $p = 0.003$) as compared to the reference group.

Secondary analysis (data analyses by MCI sub types)

Comparison of aMCI with controls—Moderate caloric intake was not associated with an increased odds of having aMCI (OR 1.40, 95% CI 0.80–2.44, $p = 0.24$). High caloric intake was associated with a significantly increased odds of having aMCI (OR 2.45, 95% CI 1.45–4.14, $p < 0.001$, Table 2).

Comparison of naMCI with controls—Moderate caloric intake was associated with decreased odds of having naMCI (OR 0.35, 95% CI 0.14–0.87, $p = 0.024$); however, the results were no longer significant after adjustment were made for BMI (OR 0.40, 95% CI 0.15–1.04, $p = 0.059$). High caloric intake (>2,143 kcals per day) was associated with a non-

significant, marginally increased odds of having naMCI (OR 1.06, 95% CI 0.51–2.18, $p = 0.89$, Table 2).

Stratified analyses by APOE $\epsilon 4$ genotype status

As expected, the proportion of individuals with an *APOE* $\epsilon 4+$ allele was higher in the MCI group than among normal controls. Having both characteristics at the same time (i.e., *APOE* $\epsilon 4+$ status and high caloric intake) was associated with significantly increased odds of having MCI (OR 3.49, 95% CI 1.53–7.98); this finding was primarily driven by association with aMCI (OR 5.23, 95% CI 1.96–13.9). Being *APOE* $\epsilon 4-$ and engaging in daily high caloric intake was associated with marginally significant odds of having MCI (OR 1.73, 95% CI 1.00–2.99, $p = 0.048$). Details of the findings are displayed in Table 3.

DISCUSSION

In this population-based case-control study, we observed that moderate caloric intake was not associated with MCI, whereas high caloric intake was associated with an increased odds of having MCI. These findings were observed after adjusting for age, sex, education, medical comorbidity, depression, and BMI. A secondary analysis by MCI subtype showed a significant association between high caloric intake and the odds of having aMCI but not naMCI. Furthermore, the odds of having aMCI was more amplified among subjects that are *APOE* $\epsilon 4+$, and this finding is reminiscent of an observation made by a New York group that noted that high caloric intake was associated with higher risk of AD among *APOE* $\epsilon 4+$ study participants but not among *APOE* $\epsilon 4-$ participants [6]. The result of our primary analysis is biologically plausible and is consistent with the public health recommendations of eating and drinking in moderations [27, 28]. Furthermore, it gives empirical credence to the customary wisdom of “doing things in moderation”.

We would like to suggest the following hypothesis of chain of causality with regard to our finding of the secondary analysis i.e. high caloric intake is associated with aMCI but not non-amnesic MCI. Several reports have suggested that aMCI is very likely to be a prodromal stage of AD [29–33]; thus, the underlying pathology of aMCI may be consistent with AD pathology [34]. Furthermore, some have argued that increased caloric intake may contribute to AD pathology through oxidative stress [6, 35], which has been shown to promote intracellular accumulation of amyloid β protein by enhancing the amyloidogenic pathway [36, 37]. Therefore, this, in part, may explain why we noted an association between high caloric intake and odds of having aMCI but not naMCI.

There are alternative interpretations of the associations between high caloric intake and the odds of having aMCI while keeping in mind that recall bias is inherent in survey-based dietary assessments [38]. The FFQ that we and several others have used [39–42] is a well-tested tool albeit of variable validity, especially in the elderly [41]. Thus, one potential explanation for our study finding is that the self-reported food frequency may be skewed towards over-reporting in the aMCI group. Although aMCI, by definition, is associated with memory problems, this may not be the sole explanation of our findings. Depression impacts FFQ recall [43]; however, we have adjusted for depression in all the analyses that compared the caloric consumption between MCI and the cognitively normal group. Despite the above competing explanations, one cannot rule out the possibility that subjects with MCI or subjects who are at risk of developing MCI [7] may consume more calories than controls. This can only be confirmed by using objective measures of caloric expenditure as consistently advocated by one of the coauthors (JAL) [44].

Our study did not address mechanism of action. However, the possible beneficial impact of caloric restriction without malnutrition has been consistently reported in rodents [45], monkeys [46], and human subjects [47].

The findings of our study should be interpreted within the context of the limitations of the study. The first limitation pertains to study design. Since this was a cross-sectional study, we cannot determine the direction of causality between the hypothesized exposure of interest (i.e., caloric intake) and the hypothesized outcome of interest (i.e., MCI). Second, like any survey-based study, recall bias is a potential limitation. This is even more relevant to participants with MCI; however, there are two steps we have taken to explore recall bias and the findings are reassuring. First, in the past, we had conducted a sensitivity analysis on this sample and found out that excluding subjects that scored in the lowest 5th percentile on memory domain and subjects with memory problems did not affect the results of the study [5]. Second, at our center, neither the participant nor the research personnel knew the case-control status of the participant at the time of completion of the FFQ. This likely minimized bias, but could not eliminate it. Third, in the past, we had reported that the test-retest correlations for surveys that assessed physical exercise were similar among subjects with normal cognition and MCI in this same population; while this is reassuring, it may not be relevant to the FFQ [48].

In summary, little is known about the association between caloric intake and MCI [7]. Thus, our work contributes to the growing research interest in this area. In any case-control study, one cannot be certain of the direction of causality. Our finding should be considered tentative until future studies confirm or disprove our observations.

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Table 1

Demographic characteristics of study participants

Variable	Normal (<i>n</i> = 1,072)	MCI (<i>n</i> = 161)	<i>P</i>
Men, <i>n</i> (%)	546 (50.9)	95 (59.0)	0.063
Age, y ^a	79 (75, 84)	83 (78, 86)	<0.001
Education, y ^a	13 (12, 16)	12 (12, 15)	0.001
>12, <i>n</i> (%)	451 (42.1)	84 (52.2)	
BDI-II Depression (13) ^b	51 (4.8)	21 (13.4)	<0.001
Charlson Index ^a	3 (1, 5)	4 (2, 6)	<0.001
Body mass index (kg/m ²) ^{a,c}	27.1 (24.2, 30.3)	26.5 (23.8, 29.6)	0.053
30 kg/m ² (obese), <i>n</i> (%)	289 (27.6)	32 (21.5)	
<i>APOE</i> ε4+, <i>n</i> (%) ^d	223 (21.4)	49 (31.6)	0.007
Energy (kcal) ^a	1,792 (1,352, 2,330)	2,060 (1,506, 2,681)	0.001
600 to <1,526, <i>n</i> (%)	369 (34.4)	42 (26.1)	
1,526 to 2,143	368 (34.3)	44 (27.3)	
>2,143	335 (31.3)	75 (46.6)	

^aMedian (interquartile range);^b23 patients missing BDI-II Depression (19 Normal, 4 MCI);^c37 patients missing BMI (25 Normal, 12 MCI);^d38 patients missing *APOE* ε4 status (32 Normal, 6 MCI).

Table 2

Caloric intake and the odds of having MCI

Energy (in kcal)	OR (95% CI) ^a	<i>p</i> ^a	OR (95% CI) ^b	<i>p</i> ^b
<i>Total MCI</i>				
600 to <1,526	1.00 (Reference)		1.00 (Reference)	
1,526 to 2,143	1.00 (0.63, 1.59)	0.99	0.87 (0.53, 1.42)	0.57
>2,143	1.84 (1.20, 2.82)	0.006	1.96 (1.26, 3.06)	0.003
<i>aMCI</i>				
600 to <1,526	1.00 (Reference)		1.00 (Reference)	
1,526 to 2,143	1.40 (0.80, 2.44)	0.24	1.15 (0.64, 2.04)	0.64
>2,143	2.45 (1.45, 4.14)	<0.001	2.44 (1.44, 4.15)	0.001
<i>naMCI</i>				
600 to <1,526	1.00 (Reference)		1.00 (Reference)	
1,526 to 2,143	0.35 (0.14, 0.87)	0.024	0.40 (0.15, 1.04)	0.059
>2,143	1.06 (0.51, 2.18)	0.89	1.26 (0.59, 2.72)	0.55

^a Adjusted for age, sex, education, BDI-II Depression, and medical comorbidity;^b Additionally adjusted for body mass index.

Table 3Caloric intake and the odds of having MCI: stratified by *APOE* $\epsilon 4$ allele status

Energy (in kcal)	OR (95% CI) ^a	<i>p</i> ^a	OR (95% CI) ^b	<i>p</i> ^b
<i>APOE</i> $\epsilon 4^-$				
<i>Total MCI</i>				
600 to <1,526	1.00 (Reference)		1.00 (Reference)	
1,526 to 2,143	0.99 (0.57, 1.72)	0.97	0.86 (0.48, 1.55)	0.61
>2,143	1.65 (0.97, 2.80)	0.062	1.73 (1.00, 2.99)	0.048
<i>APOE</i> $\epsilon 4^-$ <i>aMCI</i>				
600 to <1,526	1.00 (Reference)		1.00 (Reference)	
1,526 to 2,143	1.29 (0.67, 2.50)	0.45	1.08 (0.55, 2.12)	0.83
>2,143	1.82 (0.95, 3.48)	0.070	1.76 (0.91, 3.39)	0.091
<i>APOE</i> $\epsilon 4^-$ <i>naMCI</i>				
600 to <1,526	1.00 (Reference)		1.00 (Reference)	
1,526 to 2,143	0.29 (0.09, 0.94)	0.038	0.33 (0.10, 1.13)	0.078
>2,143	1.45 (0.62, 3.38)	0.39	1.70 (0.69, 4.19)	0.25
<i>APOE</i> $\epsilon 4^+$				
<i>Total MCI</i>				
600 to <1,526	1.00 (Reference)		1.00 (Reference)	
1,526 to 2,143	1.65 (0.66, 4.14)	0.29	1.47 (0.55, 3.96)	0.44
>2,143	2.92 (1.32, 6.46)	0.008	3.49 (1.53, 7.98)	0.003
<i>APOE</i> $\epsilon 4^+$ <i>aMCI</i>				
600 to <1,526	1.00 (Reference)		1.00 (Reference)	
1,526 to 2,143	2.52 (0.83, 7.61)	0.10	1.98 (0.61, 6.36)	0.25
>2,143	4.67 (1.77, 12.3)	0.002	5.23 (1.96, 13.9)	<0.001
<i>APOE</i> $\epsilon 4^+$ <i>naMCI</i>				
600 to <1,526	1.00 (Reference)		1.00 (Reference)	
1,526 to 2,143	0.71 (0.13, 3.88)	0.69	0.90 (0.15, 5.22)	0.90
>2,143	0.53 (0.10, 2.87)	0.46	0.73 (0.13, 4.24)	0.73

^a Adjusted for age, sex, education, BDI-II Depression, and medical comorbidity;^b Additionally adjusted for body mass index.