

## FEATURED ARTICLE

# Dietary fatty acids and risk of Alzheimer's disease and related dementias: Observations from the Washington Heights-Hamilton Heights-Inwood Columbia Aging Project (WHICAP)

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## Abstract

**Introduction:** High dietary intake of long chain, polyunsaturated fatty acids is associated with lower Alzheimer's disease (AD) risk.

**Methods:** Washington Heights-Hamilton Heights-Inwood Columbia Aging Project is a multiethnic, prospective observational study of aging and dementia among elderly ( $\geq 65$  years). Dietary intake was measured using a food frequency questionnaire. Dietary short-, medium-, and long-chain fatty acid intakes were categorized by number of carbons and double bonds. Consensus AD diagnoses were made. Associations between AD risk and dietary fatty acid and cholesterol intakes were estimated using multivariable Cox proportional hazards regression models.

**Results:** Of 2612 multiethnic women (67%) and men (baseline age 76.3 [6.4] years), 380 developed AD over an average 4.5 years follow-up. Lower risk of AD was associated with increasing intakes of docosahexaenoic acid (DHA; hazard ratio [HR] = 0.73, 95% confidence interval [CI]: 0.57 to 0.95,  $P = 0.018$ ) and eicosapentaenoic acid (EPA; HR = 0.74, 95% CI: 0.57 to 0.95,  $P = 0.021$ ), and longer AD-free survival ( $P < 0.05$ ).

**Discussion:** Higher intake of DHA and EPA are protective for AD.

## KEYWORDS

Alzheimer's disease and related dementias (ADRD), cholesterol, DHA, diet, EPA, fatty acids, omega-3, risk factor

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## 1 | INTRODUCTION

High dietary intake of long chain, polyunsaturated fatty acids (LCPUFAs) is associated with lower risk for Alzheimer's disease (AD) and related dementias (ADRD) in epidemiological and clinical research studies. High intake of fish<sup>1-3</sup> and unsaturated fatty acids<sup>2,4-6</sup> have been associated with reduced ADRD risk and/or cognitive decline. Data also suggest that intake of the Mediterranean diet or healthy dietary patterns that are high in LCPUFAs are also protective for ADRD and ADRD mortality.<sup>7-9</sup> In a clinical trial of omega-3 dietary supplements (1.7 g docosahexaenoic acid [DHA] + 0.6 g eicosapentaenoic acid [EPA]), there was a reduction in cognitive decline among those with a baseline Mini-Mental State Examination (MMSE) > 27 within the first 6 months.<sup>6</sup> Despite the focus on and evidence for dietary LCPUFAs in association with ADRD, the associations between dietary intake of other fatty acids that differ by chain length and/or degree of saturation and ADRD risk is underexplored.

Disentangling associations of multiple, heterogeneous dietary components, both traditional nutrients and non-nutrients, with human health, has sometimes been addressed using biochemical classifications. Dietary fat, one macronutrient of three in the human diet, is comprised of several very different molecules, primarily cholesterol and other sterols, fatty acids, and triglycerides (glycerol + fatty acids).<sup>10</sup> Dietary fatty acids (carboxylic aliphatic acids with the general formula  $H(CH_2)_nCOOH$ ), have been of utmost interest because of their chemical and functional diversity.<sup>11</sup> Fatty acids differ in chain length (number of carbons) and degree of saturation or hydrogenation (number of double bonds). These characteristics contribute to distinct chemical properties, biological functionality, and physiological roles.<sup>12,13</sup> As a result, dietary fatty acids have been chemically classified based on length (short, medium, and long carbon chains), and degree of hydrogen saturation, in addition to the presence of specific functional groups at the carboxylic end. Notably, there is not 100% agreement as to what carbon chain lengths constitute the definitions of short, medium, and long.<sup>10,12,14</sup>

LCPUFAs have been of interest because they are concentrated in certain foods such as cold-water fish, vegetable oils, nuts, and seeds, and are highly bioactive molecules that are associated with human health and disease.<sup>15,16</sup> Once incorporated into cell membranes, LCPUFAs confer enhanced flexibility, in contrast to saturated fatty acids (FAs) and cholesterol, which contribute to a more rigid cell membrane. LCPUFAs also function as cell signaling molecules, are involved in neurotransmitter biosynthesis, and regulate membrane-bound enzymes and eicosanoid production. Certain LCPUFAs, such as DHA, are highly concentrated in the human retina and brain.<sup>16</sup>

Despite the distinct chemical properties and potential health benefits of distinct individual or classes of fatty acids, few concrete public health recommendations have been made. In the United States, as of the most recent update in 2005, dietary reference intakes (DRI) for adults age 18 years and older exist for total fat (20% to 35% of total energy intake), omega-6 PUFA (5% to 10% of total energy intake), and

### RESEARCH IN CONTEXT

1. Systematic review: Dietary intake is a modifiable lifestyle factor for Alzheimer's disease and related dementias (ADRD). Long chain fatty acids, such as those found in fish, nuts and seeds, and plant oils are associated with reduced ADRD risk. From a nutritional biochemistry perspective, little is known about possible differential associations of ADRD and fatty acids by carbon chain length or degree of saturation.
2. Interpretation: Population-based data from >2600 participants in the multiethnic Washington Heights-Hamilton Heights-Inwood Columbia Aging Project, suggest an exclusive association between ADRD-free survival and high intake of two omega-3 fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), compared to intake of other saturated or unsaturated long chain-, medium-, or short-chain fatty acids, total fat, or cholesterol.
3. Future Directions: These data support the need for dietary intake recommendations for EPA and DHA because they are insufficiently produced by the human body and are modifiable risk factors that promote ADRD-free survival.

omega-3 PUFA (0.6% to 1.2% of total energy intake). Dietary intake of total cholesterol, trans-fatty acids, and saturated fatty acids are recommended to be "as low as possible while consuming a nutritionally adequate diet."<sup>17</sup> Adequate intake (AI) guidelines, defined when there is insufficient evidence to set a DRI, were set for adults age 51 years and older for the essential omega-6 fatty acid, alpha-linoleic acid (men: 14 g/d, women: 11 g/d) and the omega-3 fatty, alpha-linolenic acid (men: 1.6 g/d, women: 1.1 g/d).<sup>17</sup> Given the low in vivo conversion efficiency of dietary alpha-linoleic and alpha-linolenic acid to DHA and EPA, some also deem DHA and EPA to be essential fatty acids.<sup>16</sup>

Due to the paucity of literature on more in-depth exploration of fatty acids, we explored the association between dietary fatty acid and cholesterol intake with AD and ADRD risk in a multiethnic, longitudinal, population study, the Washington Heights-Hamilton Heights-Inwood Columbia Aging Project (WHICAP). Our hypothesis was that LCPUFAs are more likely protective for AD and ADRD than short- or medium-chain fatty acids, and that saturated fatty acids and cholesterol increase risk for AD. To disentangle various classifications of dietary fatty acids that are often used, we considered three different fatty acid classifications based on published definitions of short-, medium-, and long-chain fatty acids, as well as degree of saturation. Intake of certain individual fatty acids was also considered.

## 2 | METHODS

### 2.1 | Study population

The WHICAP study includes participants in two related cohorts who were recruited in 1992 and 1999. Participants were recruited from a probability sample of Medicare beneficiaries residing in northern Manhattan, New York. At study entry, a physician elicited each participant's medical and neurological histories and conducted standardized physical and neurological examinations. Each participant also underwent a structured in-person interview including an assessment of health and function, and a neuropsychological battery.<sup>18</sup> A global summary score based on the Clinical Dementia Rating was assigned. Participants were followed at intervals of  $\approx 1.5$  years, repeating the baseline examination and consensus diagnosis.

### 2.2 | ADRD diagnosis

A consensus diagnosis for the presence or absence of incident ADRD was made at a diagnostic conference attended by neurologists and neuropsychologists, using the neuropsychological battery of tests and evidence of cognitive deficit (based on the neuropsychological scores), evidence of impairment in social or occupational function (as assessed by the Blessed Dementia Rating Scale, the Schwab and England Activities of Daily Living Scale, and the physician's assessment), and evidence of cognitive and social/occupational function decline compared to the past, as required by the Diagnostic and Statistical Manual of Mental Disorders (Third Edition Revised). The type of dementia was subsequently determined. For the diagnosis of probable or possible AD, the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer Disease and Related Disorders Association were used. Because, according to the criteria, stroke does not preclude the diagnosis of AD (unless cerebrovascular disease is considered the primary cause of the dementia), the diagnosis of AD with concomitant stroke was also assigned. Therefore, dementia cases with cerebrovascular damage could be classified either in the non-AD dementia category or in the AD category. Diet data were not available to the diagnostic consensus panel and were not considered in the diagnostic process. The diagnostic consensus conferences took place on a continuous basis from the beginning of the study (ie, every few months as completed participants' evaluations were accumulated). Because WHICAP has been ongoing for more than 25 years, different neurologists and neuropsychologists have been participating at the consensus diagnoses over time, but always using the same diagnostic criteria.

### 2.3 | Dietary data

Average food consumption during the year before the baseline assessment was obtained in the majority of the cohort via one administration of a 61-item version of the semi-quantitative Harvard food frequency questionnaire (FFQ)<sup>19</sup> (Channing Laboratory, Cambridge,

Massachusetts). Trained interviewers administered the FFQ in English or Spanish. Validity and reliability of these FFQs to estimate nutrient intake among elderly participating in WHICAP has been evaluated.<sup>20</sup> The daily intake of nutrients, with a focus on individual fatty acids and classes of fatty acids, was estimated by multiplying the intake frequency of each portion of every food listed on the FFQ by the nutrient content of the specified portion. Dietary intake was adjusted for total energy intake.

#### 2.3.1 | Dietary fatty acid categories

Dietary fatty acids were classified in three ways—Classifications 1, 2, and 3—based on published definitions of short, medium, and long chains, as well as degree of saturation (see Table 1).<sup>10,11</sup> In addition, given the higher prevalence of certain fatty acids and fatty acid groups in the human diet, desired comparisons of PUFAs with LC saturated FAs, and the goodness of the nutrient data base, we evaluated certain fatty acids or groups of fatty acids individually. These included: total saturated fats, total PUFAs, total monounsaturated fatty acids, total omega-3 and omega-6 fatty acids, two omega-3 fatty acids, EPA (20:5), and DHA (22:5); the monounsaturated fat, oleic acid (18:1); and two long-chain saturated fatty acids, palmitate (16:0) and stearate (18:0). Chain length only is considered in Classifications 1 and 2. Number of double bonds is considered in addition to chain length with evaluation of Classification 3, and the individual fatty acids or groups.

### 2.4 | Covariates

A variety of potential covariates were evaluated in relation to analyses of dietary fatty acid intake and AD. Information about recruitment cohort, age, sex, education, race/ethnicity, body mass index (calculated as weight in kilograms divided by height in meters squared), and smoking status were obtained from baseline interviews. Daily total energy intakes were calculated from the baseline FFQ administered at one time point. A modified version of the Charlson Comorbidity Index<sup>21</sup> (hereafter referred to as the "comorbidity index") included items for myocardial infarction, congestive heart failure, peripheral vascular disease, hypertension, chronic obstructive pulmonary disease, arthritis, gastrointestinal disease, mild liver disease, diabetes, chronic renal disease, and systemic malignancy from the initial visit. All items received weights of 1, with the exception of chronic renal disease and systemic malignancy, which were weighted 2. The comorbidity index was treated as a continuous variable. Possession of the apolipoprotein E (APOE) $\epsilon 4$  allele was also considered.

### 2.5 | Statistical analyses

Independent samples *t* tests were used to compare incident ADRD versus no ADRD on a variety of baseline continuous sociodemographic factors. Chi-square tests were used for categorical variables. Multivariate Cox proportional hazards models were used to evaluate

**TABLE 1** Dietary fatty acid classifications based on carbon chain length and number of double bonds, and individual fatty acids and fatty acid groups evaluated in association with Alzheimer's disease and related dementia risk and survival in the Washington Heights-Inwood Columbia Aging Project

Classification	Short chain (carbon number)	Medium chain (carbon number)	Long chain (carbon number)	Very long chain (carbon number)
1	2-6	8-14	≥16	NA
2	2-4	6-12	14-22	24-26
3 <sup>a</sup>	NA	NA	Saturated: 12+, 14+, 16+ Unsaturated: 16+	
<b>Individual fatty acids or groups</b>				
Omega-3 <sup>b</sup> fatty acids, total				
Eicosapentaenoic acid (EPA, 20:5 <sup>c</sup> )				
Docosahexaenoic acid (DHA, 22:5)				
Omega-6 fatty acids, total				
Monounsaturated fatty acids, total				
Oleic acid (18:1)				
Long-chain saturated fatty acids, total				
Palmitic acid (16:0)				
Stearic acid (18:0)				
Long-chain polyunsaturated fatty acids, total				

<sup>a</sup>Chain length only is considered with Classifications 1 and 2. Number of double bonds is considered in addition to chain length with evaluation of Classification 3 and the Individual fatty acids or group.

<sup>b</sup>The number refers to positioning of the first double bond in proximity to the fatty acid methyl group.

<sup>c</sup>The ratio of the number of carbons to the number of double bonds.

the relationships between tertiles of baseline dietary fatty acid and cholesterol intakes and incident AD and ADRD, after confirmation that the assumption of proportional hazards in the Cox regression models was met. Tertiles were used due to skewness of these dietary intake variables. Quartiles were also evaluated and found to be similar in all essential aspects. Daily baseline dietary intake of short-, medium-, and long-chain fatty acids were summed according to the classification of interest. This was easy to do, as intakes of individual fatty acids (and their chemical formulas) are included in the Harvard nutrient data base. Due to high correlations among dietary fatty acids, only single fatty acid classification categories, eg, short chain, were included in regression models. In addition, we evaluated intake of fatty acids in the manner of dose versus as proportion of total dietary fat intake. Given published data on the nutraceutical role of certain fatty acids in brain health and ADRD, this was deemed the most appropriate approach and in line with our hypothesis. Of the covariates considered, those that were significant in age-adjusted models at  $P < 0.05$  were included in multivariable regression models. Thus, covariates included age, education, race, sex, APOE $\epsilon$ 4 allele possession, current smoking, total energy intake, and comorbidities.

### 3 | RESULTS

At baseline, there were  $N = 2647$  participants without dementia and with dietary intake information. Of these,  $N = 2612$  participants

(67.4% women) reported an average daily energy intake of 500 to 3500 kilocalories (a range deemed to be "healthy"). Participants were followed for an average of 4.5 years. Over this follow-up period,  $N = 406$  developed ADRD (12 008 person-years at risk; incidence rate of 3.3%), and of these,  $N = 380$  (93.6% of ADRD cases) developed AD (11 869 person-years at risk). Baseline characteristics of WHICAP participants with dietary intake information are presented in Table 2. Notably, at baseline, compared to those who remained free of ADRD, higher age and lower education were associated with incident ADRD. In addition, the representation of various racial groups was not uniform. Dietary intake of total fat and cholesterol in the sample were comparable to those typically reported in other aging cohort studies as evidenced by Table 3 median intakes by tertile.

Consideration of different fatty acid classifications based on chain length and degree of saturation did not shed additional light on AD risk associations. Of all fatty acid categories evaluated, intakes of DHA and EPA were related to the lowest AD risk and longest ADRD-free survival ( $P < 0.05$ , Table 3, Figures 1 and 2). A 27% lower risk of AD was observed for DHA and 26% lower AD risk for EPA, comparing intakes in the highest tertile compared to the lowest tertile. Intake of dietary cholesterol was associated with a 38% higher risk of AD ( $P < 0.05$ ). Intake of very long chain fatty acids (24 to 26 carbons) was not represented in these data. Results associating fatty acids and cholesterol to ADRD (all dementias) were similar in all essential aspects to those for AD.

**TABLE 2** Washington Heights-Inwood Columbia Aging Project sample baseline characteristics of those who developed Alzheimer's disease and related dementia (ADRD) and those who remained ADRD-free over the course of longitudinal follow-up

Variable	ADRD (406)	No ADRD (2206)	All (2612)	ADRD vs no ADRD P-value
Women, n (%)	278 (68.5)	1483 (67.2)	1761 (67.4)	0.622
Age (years), mean (SD)	78.8 (6.8)	75.9 (6.3)	76.3 (6.4)	<0.0001
Ethnicity				
White, n (%)	52 (12.8)	678 (30.7)	730 (27.9)	<0.0001
Black, n (%)	124 (30.5)	715 (32.4)	839 (32.1)	
Hispanic, n (%)	226 (55.7)	782 (35.4)	1008 (38.6)	
Other, n (%)	4 (1.0)	31 (1.4)	35 (1.3)	
Any APOE $\epsilon$ 4 allele, n (%) <sup>a</sup>	120 (31.7)	514 (26.9)	634 (27.6)	0.056 <sup>a</sup>
Education (years), mean (SD) <sup>b</sup>	7.5 (4.7)	10.5 (4.7)	10.0 (4.8)	<0.0001 <sup>b</sup>
Body mass index (kg/m <sup>2</sup> )	27.3 (5.8)	27.8 (5.3)	27.7 (5.4)	0.168
Energy intake (kilocalories), mean (SD)	1488.4 (546.3)	1433.8 (494.0)	1442.25 (502.7)	0.0439 <sup>c</sup>
Smoking, n (%)	48 (11.8)	252 (11.4)	300 (11.5)	0.8166
Number of comorbidities, mean (SD)	2.3 (1.6)	2.2 (1.5)	2.2 (1.5)	0.3739 <sup>d</sup>
CDR > 0, n (%)	173 (44.5)	339 (15.6)	512 (20)	<0.001

<sup>a</sup>2293 observations available.<sup>b</sup>2609 observations available.<sup>c</sup>Of those with an average baseline daily energy intake of 500 to 3500 kilocalories.<sup>d</sup>2366 observations available.

Abbreviations: APOE, apolipoprotein E; CDR, Clinical Dementia Rating; SD, standard deviation.

Briefly, if one considers results of  $P \geq 0.05$  to  $< 0.10$ , there was a suggested lower AD risk with higher dietary intake of all long chain unsaturated and omega-3 FAs; and higher risk with increasing dietary intake of monounsaturated fatty acids and total fat.

## 4 | DISCUSSION

In this prospective, multiethnic population study, and in line with others published, we observed that two well-known LCPUFAs, EPA and DHA, were protective against the development of AD and ADRD, after adjusting for multiple covariates. Previously in this population, a dietary pattern rich in omega-3 and omega-6 PUFA, vitamin E, and folate, and lower in saturated fatty acids (SFA) and vitamin B12, was found to be protective for AD. This was coincident with high intakes of salad dressing, nuts, fish, tomatoes, poultry, cruciferous vegetables, fruits, and dark and green leafy vegetables and low intake of high-fat dairy, red meat, organ meat, and butter. A "Mediterranean-type" diet, also high in LCPUFAs, has been related to lower risk of AD in WHICAP.<sup>7,8,22-25</sup> Our data confirm that higher intakes of LCPUFAs may be more important early in the course of disease.<sup>26</sup>

Observations from WHICAP are confirmatory of other epidemiologic reports suggesting the specific importance of EPA and DHA, compared to total PUFA intake or intake of other long-chain fatty acids. EPA and DHA are conditionally essential fatty acids, and inefficiently synthesized by the human body. Thus, optimal intake of these food components must be achieved via the diet, and their importance is underscored in relation to modifiable risk reduction for ADRD.

Perhaps it is not surprising that multiple epidemiologic studies indicate the importance of LCPUFAs for the human body and especially for the brain. An average healthy EPA- and DHA-containing human diet results in high brain levels of DHA; and DHA is the most abundant omega-3 LCPUFA in the brain contributing up to 6% of the brain's dry weight.<sup>27</sup> Omega-3 LCPUFA, primarily EPA and DHA, are important for cell membrane synthesis, and particularly for the nervous system.<sup>28</sup> DHA and EPA are important for neuronal cell integrity, synaptic health, synaptic plasticity,<sup>29</sup> and myelin synthesis.<sup>30</sup> They are primary ingredients for neural cell structure and function.<sup>29</sup>

In the brain, as an integral cell membrane component, DHA is responsible for optimal membrane-protein interaction in signal transduction,<sup>31</sup> enhances expression of genes such as synuclein,<sup>32</sup> and plays an important role in neurodegeneration. Presence of DHA in the cell membrane represents aspects of a physiological lipid regulatory cascade. Splicing of the transmembrane amyloid precursor protein (APP) in neuronal cells is influenced by cell membrane lipid composition. This ultimately influences the creation of the well-characterized amyloid beta ( $A\beta$ )40 and -42 oligomers that comprise brain amyloid deposits and are differentially present and diagnostic in the cerebrospinal fluid of those with mild cognitive impairment and AD.<sup>33</sup> Data from WHICAP have shown that higher dietary intake of omega-3 PUFA is associated with lower plasma levels of  $A\beta$ 42, a profile linked with lower risk of incident AD and slower cognitive decline.<sup>34</sup> In addition, the APP-derived  $A\beta$  that contributes to formation of amyloid deposits is a natural regulator of lipid homeostasis,<sup>30</sup> represses cholesterol production, and stimulates the production of other lipids.<sup>35</sup> DHA also affects cholesterol metabolism.<sup>36</sup> Dietary cholesterol increases and

**TABLE 3** Individual Cox proportional hazards models evaluating dietary intake of fatty acids by category, individual fatty acids, and cholesterol in relationship to the outcome, AD

Tertiles of fatty acid intake <sup>a</sup>				
	T1	T2	T3	P for trend
<b>Classification 1</b>				
<b>Short-chain fatty acids</b>				
Median (g/d)	0.16	0.41	0.75	
Incident AD	111	117	150	
RR (95% CI)	1.0 (REF)	1.14 (0.88, 1.47)	1.52 (1.19, 1.95)	0.0007
Age-adj HR <sup>b</sup>	1.0 (REF)	1.05 (0.81, 1.37)	1.24 (0.97, 1.59)	0.0835
Multi-adj HR <sup>c</sup>	1.0 (REF)	1.08 (0.83, 1.42)	1.14 (0.86, 1.52)	0.3737
<b>Medium-chain fatty acids</b>				
Median (g/d)	0.90	1.83	3.17	
Incident AD	117	117	144	
RR (95% CI)	1.0 (REF)	1.03 (0.80, 1.33)	1.44 (1.13, 1.84)	0.0035
Age-adj HR	1.0 (REF)	0.90 (0.70, 1.17)	1.16 (0.90, 1.48)	0.2185
Multi-adj HR <sup>a</sup>	1.0 (REF)	0.88 (0.67, 1.16)	1.09 (0.80, 1.49)	0.5900
<b>Long-chain fatty acids</b>				
Median (g/d)	12.86	20.39	31.02	
Incident AD	125	118	135	
RR (95% CI)	1.0 (REF)	0.96 (0.75, 1.24)	1.26 (0.99, 1.61)	0.0659
Age-adj HR	1.0 (REF)	0.94 (0.73, 1.21)	1.14 (0.89, 1.46)	0.2963
Multi-adj HR <sup>a</sup>	1.0 (REF)	0.92 (0.69, 1.22)	1.20 (0.83, 1.74)	0.3450
<b>Classification 2</b>				
<b>Short-chain fatty acids</b>				
Median (g/d)	0.100	0.270	0.490	
Incident AD	110	118	150	
RR (95% CI)	1.0 (REF)	1.09 (0.84, 1.41)	1.48 (1.15, 1.89)	0.0017
Age-adj HR	1.0 (REF)	0.99 (0.76, 1.28)	1.18 (0.92, 1.51)	0.1788
Multi-adj HR <sup>a</sup>	1.0 (REF)	1.02 (0.78, 1.34)	1.09 (0.81, 1.45)	0.5685
<b>Medium-chain fatty acids</b>				
Median (g/d)	0.340	0.740	1.320	
Incident AD	117	113	148	
RR (95% CI)	1.0 (REF)	1.02 (0.79, 1.32)	1.40 (1.10, 1.78)	0.0065
Age-adj HR	1.0 (REF)	0.89 (0.68, 1.15)	1.14 (0.89, 1.46)	0.2623
Multi-adj HR <sup>a</sup>	1.0 (REF)	0.91 (0.69, 1.20)	1.05 (0.78, 1.41)	0.7250
<b>Long-chain fatty acids</b>				
Median (g/d)	13.66	21.62	32.74	
Incident AD	128	113	137	
RR (95% CI)	1.0 (REF)	0.89 (0.69, 1.15)	1.26 (0.99, 1.61)	0.0616
Age-adj HR	1.0 (REF)	0.88 (0.69, 1.14)	1.14 (0.89, 1.45)	0.3097
Multi-adj HR <sup>a</sup>	1.0 (REF)	0.90 (0.67, 1.20)	1.23 (0.85, 1.79)	0.2751
<b>Classification 3</b>				
<b>Long-chain fatty acids—12 carbons, saturated</b>				
Median (g/d)	7.98	13.55	21.65	
Incident AD	121	109	148	
RR (95% CI)	1.0 (REF)	0.86 (0.66, 1.12)	1.44 (1.13, 1.83)	0.0029

(Continues)



**TABLE 3** (Continued)

Tertiles of fatty acid intake <sup>a</sup>				
	T1	T2	T3	P for trend
Age-adj HR	1.0 (REF)	0.79 (0.61, 1.02)	1.21 (0.95, 1.54)	0.1082
Multi-adj HR <sup>a</sup>	1.0 (REF)	0.84 (0.63, 1.11)	1.30 (0.91, 1.85)	0.1670
<b>Long-chain fatty acids—14 carbons, saturated</b>				
Median (g/d)	7.79	13.28	21.23	
Incident AD	121	110	147	
RR (95% CI)	1.0 (REF)	0.86 (0.67, 1.12)	1.43 (1.12, 1.82)	0.0038
Age-adj HR	1.0 (REF)	0.78 (0.60, 1.01)	1.19 (0.93, 1.52)	0.1431
Multi-adj HR <sup>a</sup>	1.0 (REF)	0.77 (0.58, 1.03)	1.18 (0.83, 1.68)	0.4141
<b>Long-chain fatty acids—16 carbons, saturated</b>				
Median (g/d)	7.07	12.03	19.07	
Incident AD	123	108	147	
RR (95% CI)	1.0 (REF)	0.86 (0.66, 1.11)	1.39 (1.10, 1.77)	0.0065
Age-adj HR	1.0 (REF)	0.76 (0.59, 0.99)	1.17 (0.91, 1.49)	0.1831
Multi-adj HR <sup>a</sup>	1.0 (REF)	0.82 (0.62, 1.09)	1.23 (0.87, 1.76)	0.2845
<b>Long-chain fatty acids—16 carbons, unsaturated</b>				
Median (g/d)	5.11	8.05	11.84	
Incident AD	131	124	123	
RR (95% CI)	1.0 (REF)	0.99 (0.77, 1.26)	1.01 (0.79, 1.29)	0.9522
Age-adj HR	1.0 (REF)	0.95 (0.74, 1.22)	0.94 (0.73, 1.20)	0.5950
Multi-adj HR <sup>a</sup>	1.0 (REF)	0.84 (0.64, 1.10)	0.75 (0.53, 1.05)	0.0943
<b>Individual long-chain fatty acids</b>				
<b>DHA (C<sub>22</sub>H<sub>32</sub>O<sub>2</sub>)</b>				
Median (g/d)	0.06	0.11	0.24	
Incident AD	145	118	115	
RR (95% CI)	1.0 (REF)	0.79 (0.62, 1.01)	0.76 (0.59, 0.97)	0.0245
Age-adj HR	1.0 (REF)	0.78 (0.61, 1.00)	0.74 (0.58, 0.94)	0.0132
Multi-adj HR <sup>a</sup>	1.0 (REF)	0.82 (0.63, 1.05)	0.73 (0.57, 0.95)	0.0184
<b>EPA (C<sub>20</sub>H<sub>30</sub>O<sub>2</sub>)</b>				
Median (g/d)	0.020	0.030	0.090	
Incident AD	134	124	120	
RR (95% CI)	1.0 (REF)	0.74 (0.58, 0.95)	0.69 (0.54, 0.88)	0.0030
Age-adj HR	1.0 (REF)	0.75 (0.59, 0.96)	0.67 (0.52, 0.86)	0.0015
Multi-adj HR <sup>a</sup>	1.0 (REF)	0.84 (0.65, 1.09)	0.74 (0.57, 0.95)	0.0208
<b>Palmitate</b>				
Median (g/d)	4.95	8.22	12.84	
Incident AD	123	107	148	
RR (95% CI)	1.0 (REF)	0.84 (0.65, 1.09)	1.43 (1.12, 1.82)	0.0034
Age-adj HR	1.0 (REF)	0.77 (0.60, 1.00)	1.22 (0.96, 1.56)	0.0925
Multi-adj HR <sup>a</sup>	1.0 (REF)	0.78 (0.58, 1.04)	1.24 (0.87, 1.76)	0.2659
<b>Stearate</b>				
Median (g/d)	2.11	3.75	6.23	
Incident AD	126	107	145	
RR (95% CI)	1.0 (REF)	0.82 (0.63, 1.06)	1.33 (1.04, 1.69)	0.0204

(Continues)

**TABLE 3** (Continued)

Tertiles of fatty acid intake <sup>a</sup>				
	T1	T2	T3	P for trend
Age-adj HR	1.0 (REF)	0.72 (0.56, 0.93)	1.12 (0.88, 1.42)	0.3321
Multi-adj HR <sup>a</sup>	1.0 (REF)	0.75 (0.57, 1.00)	1.23 (0.87, 1.73)	0.2944
<b>Oleate</b>				
Median (g/d)	7.86	13.33	21.51	
Incident AD	127	112	139	
RR (95% CI)	1.0 (REF)	0.90 (0.70, 1.16)	1.26 (0.99, 1.61)	0.0602
Age-adj HR	1.0 (REF)	0.83 (0.64, 1.07)	1.14 (0.89, 1.46)	0.2802
Multi-adj HR <sup>a</sup>	1.0 (REF)	0.91 (0.68, 1.21)	1.37 (0.95, 1.96)	0.1049
<b>Saturated fat</b>				
Median (g/d)	8.73	14.80	23.46	
Incident AD	124	106	148	
RR (95% CI)	1.0 (REF)	0.84 (0.64, 1.08)	1.37 (1.08, 1.75)	0.0086
Age-adj HR	1.0 (REF)	0.78 (0.60, 1.02)	1.19 (0.93, 1.52)	0.1392
Multi-adj HR <sup>a</sup>	1.0 (REF)	0.82 (0.62, 1.09)	1.25 (0.88, 1.77)	0.2606
<b>Monounsaturated fats</b>				
Median (g/d)	8.77	14.73	23.50	
Incident AD	124	117	137	
RR (95% CI)	1.0 (REF)	0.938 (0.728, 1.208)	1.284 (1.005, 1.640)	0.0458
Age-adj HR	1.0 (REF)	0.866 (0.672, 1.116)	1.159 (0.906, 1.483)	0.2338
Multi-adj HR <sup>a</sup>	1.0 (REF)	0.968 (0.728, 1.288)	1.421 (0.986, 2.048)	0.0685
<b>Polyunsaturated fats</b>				
Median (g/d)	4.52	7.13	10.66	
Incident AD	135	118	125	
RR (95% CI)	1.0 (REF)	0.912 (0.712, 1.167)	0.981 (0.768, 1.252)	0.8631
Age-adj HR	1.0 (REF)	0.869 (0.679, 1.113)	0.931 (0.729, 1.190)	0.5613
Multi-adj HR <sup>a</sup>	1.0 (REF)	0.774 (0.588, 1.020)	0.764 (0.547, 1.067)	0.1142
<b>Cholesterol</b>				
Median (g/d)	125.96	205.40	316.22	
Incident AD	110	128	140	
RR (95% CI)	1.0 (REF)	1.238 (0.959, 1.599)	1.594 (1.240, 2.049)	0.0003
Age-adj HR	1.0 (REF)	1.121 (0.868, 1.449)	1.390 (1.080, 1.789)	0.0099
Multi-adj HR <sup>a</sup>	1.0 (REF)	1.146 (0.873, 1.505)	1.380 (1.009, 1.886)	0.0433
<b>Omega-3</b>				
Median (g/d)	0.63	0.96	1.40	
Incident AD	132	126	120	
RR (95% CI)	1.0 (REF)	0.957 (0.750, 1.222)	0.974 (0.760, 1.248)	0.8309
Age-adj HR	1.0 (REF)	0.949 (0.743, 1.212)	0.942 (0.735, 1.208)	0.6365
Multi-adj HR <sup>a</sup>	1.0 (REF)	0.830 (0.630, 1.093)	0.715 (0.506, 1.010)	0.0566
<b>Omega-6</b>				
Median (g/d)	3.60	5.87	8.94	
Incident AD	134	120	124	
RR (95% CI)	1.0 (REF)	0.914 (0.714, 1.170)	0.961 (0.752, 1.227)	0.7398
Age-adj HR	1.0 (REF)	0.880 (0.688, 1.126)	0.915 (0.715, 1.169)	0.4708
Multi-adj HR <sup>a</sup>	1.0 (REF)	0.765 (0.582, 1.005)	0.765 (0.550, 1.063)	0.1099

(Continues)



**TABLE 3** (Continued)

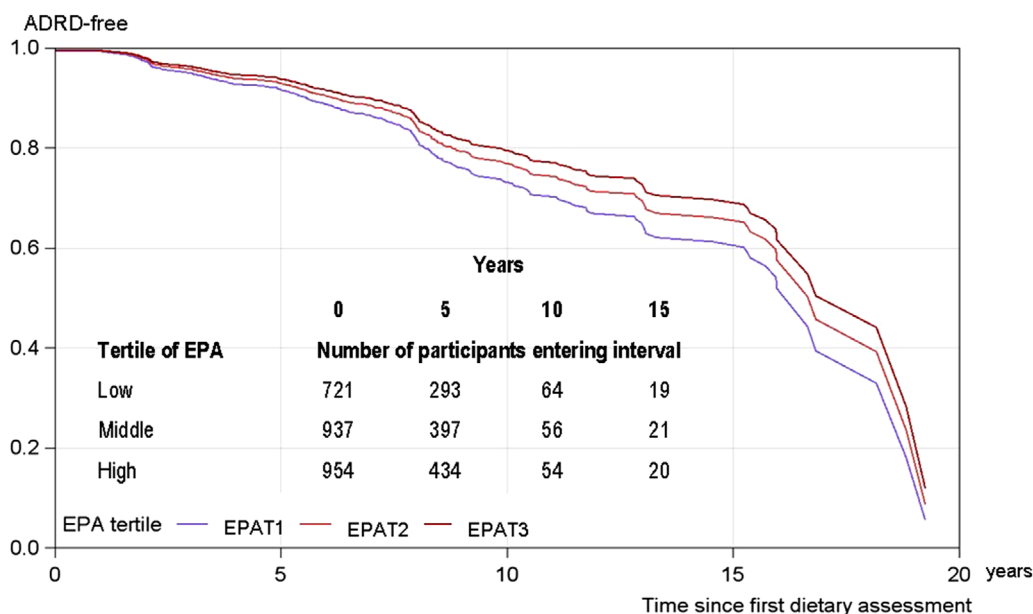
Tertiles of fatty acid intake <sup>a</sup>				P for trend
	T1	T2	T3	
<b>Total fat</b>				
Median (g/d)	25.90	41.28	62.76	
Incident AD	125	119	134	
RR (95% CI)	1.0 (REF)	0.970 (0.754, 1.248)	1.269 (0.993, 1.623)	0.0586
Age-adj HR	1.0 (REF)	0.941 (0.731, 1.210)	1.155 (0.902, 1.479)	0.2528
Multi-adj HR <sup>a</sup>	1.0 (REF)	1.010 (0.756, 1.348)	1.401 (0.961, 2.041)	0.0863
<b>DHA + EPA</b>				
Median (g/d)	0.08	0.14	0.32	
Incident AD	150	116	112	
RR (95% CI)	1.0 (REF)	0.798 (0.626, 1.017)	0.752 (0.588, 0.961)	0.0207
Age-adj HR	1.0 (REF)	0.793 (0.622, 1.010)	0.725 (0.567, 0.927)	0.0094
Multi-adj HR <sup>a</sup>	1.0 (REF)	0.827 (0.642, 1.066)	0.731 (0.565, 0.946)	0.0163

<sup>a</sup>All models include participants with an average baseline daily energy intake of 500 to 3500 kilocalories.

<sup>b</sup>Age-adjusted (age-adj) models adjusted for chronological age only.

<sup>c</sup>Multivariate models adjusted (Multi-adj) for: age, education, race, sex, APOE $\epsilon$ 4, current smoking, energy intake and the Charlson co-morbidities index.

Abbreviations: AD, Alzheimer's disease; APOE, apolipoprotein E; CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HR, hazard ratio; RR, relative risk.



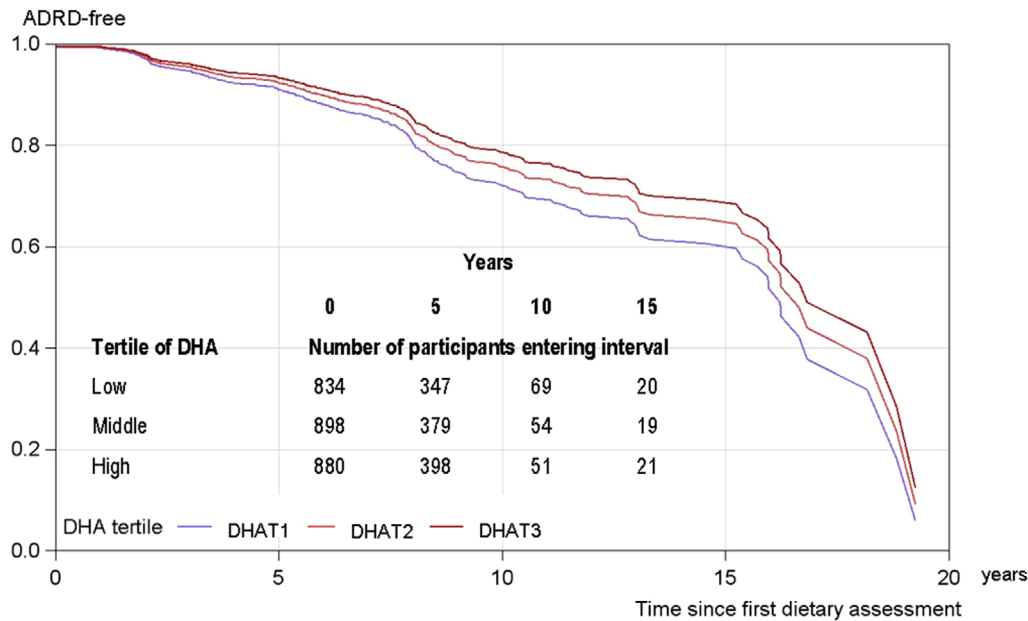
**FIGURE 1** Tertile of dietary eicosapentaenoic acid (EPA) intake by Alzheimer's disease and related dementia-free survival in Washington Heights-Inwood Columbia Aging Project.<sup>a</sup>

<sup>a</sup>Multivariate models includes participants with an average baseline daily energy intake of 500 to 3500 kilocalories and adjusted for: age, education, race, sex, apolipoprotein  $\epsilon$ 4, current smoking, energy intake, and the Charlson co-morbidities index

DHA reduces amyloid deposition,<sup>37</sup> the latter paralleling beneficial cognitive effects. Lower levels of DHA in the brain make dendrites more vulnerable to A $\beta$ ,<sup>38</sup> and impairs learning in A $\beta$ -infused rats.<sup>39</sup> Experimental studies also show that long-term dietary DHA deficiency leads to cognitive impairment<sup>40,41</sup> and that brain levels of DHA and partially cognitive performance can be restored by DHA administra-

tion. DHA is also the main antioxidant in the human brain.<sup>28</sup> Thus, there are several putative pathways through which dietary LCPUFA intake may be related to AD.

DHA and EPA are fatty acids that can be acquired by the human body in two different ways. Both can be obtained via dietary intake and both can be synthesized in vivo from alpha-linolenic acid. The human



**FIGURE 2** Tertile of dietary docosahexaenoic acid (DHA) intake by Alzheimer's disease and related dementia-free survival in Washington Heights-Inwood Columbia Aging Project.<sup>a</sup>

<sup>a</sup>Multivariate models includes participants with an average baseline daily energy intake of 500 to 3500 kilocalories and adjusted for: age, education, race, sex, apolipoprotein  $\epsilon$ 4, current smoking, energy intake, and the Charlson co-morbidities index

body cannot make alpha-linolenic acid; therefore it is essential, ie, the diet must provide it. Dietary intake of DHA and EPA is by orders of magnitude more bioavailable than in vivo synthesis from alpha-linolenic acid.<sup>16</sup> Due to the important role of DHA in brain health, the brain uses protective mechanisms if dietary intake is low. DHA turnover is very slow, thus, in the short term, a limited supply may not be problematic. However, if supply remains low or absent, other fatty acids are used instead. This has several implications, including altered membrane properties and increased propensity to inflammation. However, once DHA supply increases, these substitute fatty acids are replaced by DHA.<sup>16</sup>

As our analysis shows, it is worthwhile to note the importance of EPA and DHA compared to other dietary fatty acids and cholesterol. Cardiovascular risk factors, including both high blood and dietary cholesterol levels, in middle age, have been related to a higher risk of AD. While blood cholesterol levels are not reflective of dietary cholesterol intake, it is nonetheless of interest to evaluate both in relation to AD risk. Here we note the association of higher dietary cholesterol intake in later life, with higher AD risk, despite adjustment for cardiovascular morbidities.

While these observations from WHICAP data show protection against AD and ADRD via dietary intake of EPA and DHA, there are also published reports of no association. For example, in association with AD and ADRD, there were no associations with dietary LCPUFAs (omega-3 or omega-6) intakes over an average 9.6 years follow-up in the Rotterdam Study.<sup>42</sup> Similarly in the Veterans Affairs Normative Aging Study, there was no association observed between dietary intake of fatty fish or omega-3 LCPUFAs and cognitive change over 6 years follow-up in elderly men.<sup>43</sup> Erythrocyte omega-3 (DHA and

EPA) levels were also not longitudinally associated with ADRD in the Canadian Study of Health and Aging over  $\approx$ 10 years follow-up.<sup>44</sup> Finally, in a randomized controlled trial of 1.5 g/d of EPA + DHA, there was no effect on cognitive function in mild to moderately depressed adults at 12 weeks.<sup>45</sup>

We observed no associations between short- or medium-chain dietary fatty acids and ADRD. Short-chain fatty acids are of interest in ADRD and other neurological diseases because of evolving research on the gut-brain axis and the gut microbiome.<sup>46</sup> Certain gut bacteria produce short-chain fatty acids, which are anti-inflammatory and beneficial for the gut.<sup>47</sup> Because they are readily absorbed across the intestinal wall, they may have further systemic and central effects, and to consume more of them via the diet may be beneficial; however, there is little evidence for this. Traditionally medium-chain fatty acids have been provided to patients with malnutrition or malabsorption syndromes<sup>48</sup> because these fatty acids require no energy for absorption, use, or storage. Some data suggest medium-chain fatty acids to be beneficial for weight control and/or reducing body fat mass, both independently and because they are readily converted to ketones. As a result, they are a main component of ketogenic diets.<sup>49</sup> Medium-chain fatty acids have also been reported as potentially beneficial for ADRD and frailty, not only due to faster absorption and nutritional benefit, but also because conversion to ketones provides an alternative fuel source for the brain.<sup>48</sup>

As with any observational study of older adults, there were weaknesses of our analyses. First, the geographical representativeness of the participant sample is limited to the Washington Heights-Hamilton Heights-Inwood neighborhoods of New York City. Second, as per any community-based sample, there are losses to follow-up. Details related

to reasons for these losses in the WHICAP are published, and included refusals, unable to locate, moved, unable to schedule, and death.<sup>50</sup> Third, while we used a well-accepted dietary assessment method, there are limitations to an FFQ. Notably the food list may not contain all foods consumed by participants on a regular basis. However, there was opportunity for participants to report foods consumed at least weekly that were not included on the list. Fourth, we did not measure fatty acids in blood or other biological tissue, cell, or fluid that may be more closely related to physiological function. Fifth, only one administration of the FFQ, at baseline, was conducted, therefore change in diet over the follow-up period cannot be assessed. Sixth, results are not adjusted for multiple comparisons, given this deeper exploration of novel fatty acid classes to better understand their roles. Results for DHA and EPA are robust and supported by published literature. We acknowledge their collinearity. Finally, while attempting to identify dietary intake of individual or classes of fatty acids that may be associated with ADRD, we acknowledge that nutrients and non-nutrients are not consumed in isolation and interactions among them may have played a role. Dietary recommendations should occur within the context of whole food intake and usual diet.

Our analyses of dietary fatty acid and cholesterol intake in association with ADRD in WHICAP has a number of strengths. First, this is a very-well studied, community-based cohort of underrepresented adults living in the Upper West Side of Manhattan; and these adults had dietary total fat and cholesterol intakes comparable to those observed in other aging cohort studies. Second, we used a well-accepted, validated dietary assessment method to estimate dietary fat intake. Third, we took a novel approach to better understand dietary fatty acid intake by classifying dietary fatty acids in several ways based on chain length and degree of saturation. These classifications were based on biochemical and functional activity. Fourth, we evaluated the dose of these fatty acids contributing to daily intake. Given published data on the nutraceutical role of certain fatty acids in brain health and ADRD, this was deemed the most appropriate approach. We also adjusted all analyses for energy intake, and because dietary fat contains the most energy per gram (9 kcal/g vs 4 kcal/g for both carbohydrates and protein), these two variables are highly correlated. Finally, the diagnosis of AD and ADRD was possible via an extensive neuropsychological battery, a clinical neurological examination, with subsequent adjudication by a well-trained and expert panel of neurologists and neuropsychologists.

As of 2020, there are no dietary recommendations for DHA and EPA in the United States. While it is surmised that there is insufficient scientific evidence for making an omega-3 recommendation in the United States, data such as those presented here further support the importance of these lipids as distinct and necessary dietary components in relationship to health of the aging brain.

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