Olive Oil and Cognition: Results from the Three-City Study.

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Abstract

Background

Olive oil is a major component of the Mediterranean diet suggested to be beneficial to counteract Alzheimer's disease.

Aim

Our objective is to examine the association between olive oil use, cognitive deficit and decline in a large elderly population

Methods

We followed 6947 subjects with a brief baseline food frequency questionnaire and repeated cognitive tests. Olive oil intake was categorized as none (22.7%), moderate (use for cooking or dressing, 39.9%) and intensive (for both cooking and dressing, 37.4%). Associations between olive oil and cognitive outcomes were examined taking into account socio-economic factors, health behaviors, health measures and other dietary intakes.

Results

Participants with moderate or intensive use of olive oil compared to those who never used olive oil showed lower odds of cognitive deficit for verbal fluency and visual memory. For cognitive decline, the association with intensive use was significant for visual memory (adjusted OR=0.83, IC 95% 0.69 to 0.99) but not for verbal fluency (OR=0.85, 0.70 to 1.03).

Conclusions

This olive oil-cognition association needs to be confirmed. However, our findings already shed light on the potential importance of olive oil in the Mediterranean diet and on its beneficial effects on health.

Author Keywords olive oil ; fatty acids ; cohort study ; cognition-dementia

Introduction

A recent meta-analyses showed that a greater adherence to the Mediterranean diet was associated with lower overall mortality, mortality from cancer and cardiovascular diseases [1]. In 2006, in a northern Manhattan cohort, findings on overall diet and cognition suggest that high adherence to the Mediterranean diet (MeDi) decreases the risk of cognitive decline and Alzheimer's disease (AD) in a non demented elderly population [2] and decreases the risk of mortality in AD patients [3]. More recently in the same cohort, higher adherence to the MeDi was associated with a trend for reduced risk of developing mild cognitive impairment (MCI) and with reduced risk of MCI conversion to AD[4]. Furthermore, when investigating the combined association of diet and physical activity[5], it showed that both factors are independently associated with a reduced risk for AD. In a subsample of 1410 subjects included in the E3C Bordeaux cohort [6] with 5 year follow-up after a 24-hour dietary recall, higher adherence to MeDi was not associated with the risk for incident dementia but was associated with a slower MMSE cognitive decline. In an associated editorial, D Knopman [7] suggests that the MeDi may act on cognition through cerebrovascular mechanisms or by affecting the metabolism of the β-amyloid or the tau protein and that effects may be brought about by some components of the MeDi diet.

The so-called Mediterranean diet is characterized by a high intake of vegetables, legumes, fruits and cereals, a moderate to high intake of fish, a high monounsaturated-to-saturated fatty acids ratio and a low intake of dairy products and meat [8]. While several studies have

focused on the association between intake of fruits and vegetables or fish and cognitive outcomes other dietary habits which have been previously associated with dementia or cognitive decline (fish or omega 3 oil, fruits and vegetables) [9–20], little is known about the association between olive oil, a major component of the Mediterranean diet, and cognitive functioning.

Thus, our objective is to examine this association in a large population based study of persons aged over 65 years with a four-year follow-up of cognitive functioning.

Methods

Participants

The 3C study is a multi-center cohort study, conducted in 3 French cities- Bordeaux (SouthWest), Montpellier (South-East), and Dijon (North-East) - and designed to estimate the risk of dementia and cognitive impairment attributable to vascular factors. Persons eligible for recruitment into the study had to be i) living in these cities or their suburbs and registered on the electoral rolls, ii) aged 65 years and over, iii) not institutionalized. Between March 1999 and March 2001, 9,294 individuals, randomly drawn from electoral rolls, agreed to participate in this project. The practical organization of the different components of the data collection varied slightly between centers and during follow-up. Participants were invited to the study examination center or in a mobile center in a specially equipped vehicle or examined and interviewed at home. The detailed description of the study protocol has been published elsewhere[21]. The study protocol was approved by the Ethics Committee of the University Hospital of Kremlin-Bicêtre. Each participant signed an informed consent.

Following the screening procedure described below, we excluded 217 participants with prevalent dementia at baseline. The initial study sample was thus composed of 9077 participants. At the second round of the 3C study (2001–2002), 7919 (87.2 %) were examined again, 217 were deceased, and 941 refused or were lost-to follow-up. At the third round (2003–2004), 7053 were examined (79.6 % of the survivors after the second round), the cumulated number of deaths was 551, and 1473 refused or were lost-to follow-up. A total of 8083 (89.1%) participants had at least one follow-up examination over the 4 years. Of these 8083 subjects, 1136 did not have a dietary questionnaire (n=55) or one of the covariates, leaving 6947 subjects for statistical analysis (of which 86.0% had made 2 visits).

Dietary assessment

A brief food frequency questionnaire was administered at baseline to assess the dietary habits of the participants for nine broad categories of food: 1) meat and poultry, 2) fish (including seafood), 3) eggs, 4) milk and dairy products, 5) cereals (including bread and starches), 6) raw fruits, 7) raw vegetables, 8) cooked fruit or vegetables, 9) pulses. Frequency of consumption was recorded in six classes: never, less than once a week, once a week, 2–3 times a week, 4–6 times a week, daily. Dietary habits of the sample have been described elsewhere [22]. Participants were also invited to indicate the dietary fats that they used at least once a week for dressing, cooking, or spreading among the following list: butter, margarine, corn oil, peanut oil, sunflower or grape seed oil, olive oil, mixed oil, duck or goose fat, lard, “Vegetaline”© shortening (mainly saturated fat), colza oil, walnut oil, soya oil. Three categories of olive oil consumption were then defined: “no use”, “moderate use”: using olive oil for cooking or dressing alone and “intensive” use: using olive oil both for cooking and dressing.

Neuropsychological evaluation

The cognitive tests were administered by trained psychologists at baseline and then regularly repeated during the 4-years of follow-up. The 30-item Mini-Mental-State-Examination (MMSE) [23] was used as an index of global cognitive performance. The recognition form of the Benton Visual Retention Test (BVRT) which evaluates immediate visual memory, consists in the presentation for 10 seconds of a stimulus card displaying a geometric figure after which individuals are asked to identify the initial figure among 4 possibilities[24]. Fifteen figures are successively presented and scores range from 0 to 15. The Isaacs Set Test (IST),[25], consisting of generating words belonging to semantic categories in 30 seconds, measured mostly semantic verbal fluency abilities but also speed of verbal production.

Deficit in global cognitive functioning, visual memory and verbal fluency were defined respectively by a score below the first quartile of its distribution: 26 for the MMSE, 10 for the BVRT and 40 for the IST. Cognitive decline was defined as being in the lowest 15% of the difference between baseline score and either follow-up visit for the three tests assessed at each wave, corresponding to a loss of 3 points on the MMSE score, 9 points on IST and 3 points on BVRT. Diagnosis of prevalent cases of dementia at baseline and incident cases during the follow-up was based on a three-step procedure with an independent committee of neurologists reviewing all potential cases of dementia and is fully detailed elsewhere [26] [27].

Covariates

Socio-demographic informations recorded at baseline include age, gender, marital status, educational level (no or primary/secondary/high school/university) and income level per month (<750 €, 750–1500€, 1500–2250 €, >2250 €). Health behaviours were assessed by smoking status (non/former/current) and diet. Dietary habits include intake of fish/seafood (< once a week, once a week, ≥ twice a week), fruits and vegetables (<2 portions/day, 2 portions/day, ≥ 3 portions/day), intake of wine or other alcoholic beverages per

week (0, 1–12, 13–36, >36 g/day), coffee consumption (≤2 cups/day, 2–3 cups/day, >3 cups/day) and regular consumption (yes/no) of at least one oil rich in omega3 polyunsaturated fatty acids (PUFA) (colza, walnut or soya oils). Health factors include history of cardiovascular diseases (yes/no), hypertension (defined as having systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 85 mmHg or use of antihypertensive drugs) [28], diabetes (fasting glycaemia ≥ 7.0 mmol/L or having an anti-diabetic treatment), hypercholesterolemia (total plasma cholesterol ≥ 6.20 mmol/L or use of lipid-lowering drugs), and body mass index (BMI) categorised in three classes (normal (< 25 kg/m^2), overweight (25–30 kg/m^2) and obese (≥30 kg/m^2)). Depressive symptoms were assessed using the 16 cut-off of the Center for Epidemiological Studies-Depression scale (CES-D) [29]. Apolipoprotein E (APOE) genotype (at least 1 vs. no ε4 allele) was also available and was carried out at the Lille Genopole.

Statistical analyses

Difference in baseline characteristics according to olive oil consumption categories were tested using Chi2 tests. Logistic regression analyses were performed to estimate 1) the cross sectional association between olive oil consumption and cognitive deficit at baseline 2) the longitudinal association between olive oil consumption and cognitive decline during the follow-up. In these analyses, the adjustments for covariates were carried out in three steps. A basic model, model 0, adjusted for sex, age, study center, educational level, income and baseline cognitive score. Health behaviour and health status variables were added in the model 1. Smoking status and dietary habits were further added in the model 2. Interactions between olive oil consumption and covariates included in model 0 were tested and found to be non significant.

Finally, a sensitivity analysis was carried out., the association between olive oil intake and cognitive decline was re-examined after excluding the 4-year incident dementia cases, as dietary changes or inaccurate reporting among demented participants are common. Results of logistic regression were expressed by odds ratios (OR) with their 95% confidence intervals (CI). Analyses were carried out using SAS software (version 9.1).

Results

Participants with at least one follow-up, with no diagnosis of dementia at baseline and for whom complete data on all covariate at baseline were available were included in this analysis (n=6947). Compared with those excluded (n=2130), participants included in the analyses were more likely to be younger, with higher educational level and higher income. Controlling for these factors, a lower proportion of non users of olive oil and of subjects with poor baseline cognitive functioning was observed in participants included compared to those excluded (appendix).

Baseline characteristics of the 6947 participants as a function of olive oil consumption are described in Table 1. Among them, 1576 subjects declared no olive oil use (22.7% of total sample), 2772 declared moderate use (39.9%) only for cooking (5.8%) or dressing (34.1%), and 2599 both for cooking and dressing (intensive use, 37.4 %).

Many factors are associated with olive oil use. The particular place of education is illustrated in figure 1, more educated participants are more likely to consume olive oil compared to less educated ones.

Cross sectional association between olive oil consumption and cognitive deficit at baseline is shown in Figure 2 which presents odds ratio obtained with logistic regression (model 2). Compared to those who never used olive oil, participants with high or moderate consumption of olive oil show significantly lower odds of cognitive deficit in visual memory and verbal fluency, while no significant association is showed for global cognitive functioning.

Table 2 shows the longitudinal association between olive oil consumption and cognitive decline. After adjustment for age, sex, centre, education, income and baseline cognitive score (model 0), participants who intensively used olive oil show lower odds of cognitive decline in verbal fluency and visual memory compared to those who did not. No significant association is observed for global cognitive functioning. Further adjustment for health status (model1) has little effect on these associations. When additionally controlling for dietary habits including omega 3 oil use (model 2), having an intensive olive oil use is associated with a nearly significant risk reduction of 15 % in verbal fluency decline (OR=0.85, 95 % CI: 0.70 to 1.03) and with a 17% significant reduced risk of visual memory decline (OR=0.83, 95 % CI: 0.69 to 0.99).

Sensitivity analysis

To examine the possibility that the observed association may be due to dietary changes or inaccurate reporting among demented participants, we reanalysed the data after deleting data for the 205 persons who developed incident dementia during the 4-year follow up. Odds of lower cognitive decline associated with intensive oil remain similar to those presented for the whole sample (OR=0.88, 95% CI: 0.72 to 1.08 for verbal fluency and OR= 0.82, 95% CI: 0.68 to 0.99 for visual memory).

Discussion

The present report shows in a large non-demented elderly population that olive oil consumption habits are significantly associated with selective cognitive deficit and cognitive decline, independently of other dietary intakes and after adjusting for potential confounders. Intensive use of olive oil in diet is associated with lower odds of cognitive deficit in visual memory and verbal fluency and decline in visual memory, however the relationship is not significant when assessing global cognitive functioning with the MMSE.

Olive oil is a major component of the traditional Mediterranean diet. It has been suggested to have beneficial effect on CHD risk factors [30]. As cardiovascular risk factors have increasingly been shown to be important for dementia [31] and a greater adherence to the Mediterranean diet has been shown to reduce the incidence of Alzheimer's disease[2], it is of particular interest to investigate the association between olive oil consumption and cognitive decline in an elderly population. To our knowledge, this study is the first to investigate this relationship with olive oil in a follow-up study, thus making comparisons difficult.

Olive oil contains 70–80 % of monounsaturated fatty acids (MUFA) (oleic acid (18:1 n-9)) and 8–10% of polyunsaturated fatty acids (PUFA) (6–7 % linoleic acid and 1–2% a-linolenic acid) [32] with great variability depending on production zone, latitude, climate, variety and stage of maturity of olives when collected [33]. Recent publications on diet in dementia have specifically focused on PUFA but few examine the association with monounsaturated fatty acids (MUFA) intakes. A Spanish cross-sectional study [34] showed that a lower intake of saturated fatty acids (SFA), MUFA and cholesterol was associated with a better cognitive performance. Cross sectional analyses in an Italian cohort (ILSA) showed that MUFA intake was significantly associated with better global cognitive functions and selective attention [35]. More recently, a longitudinal analysis performed in the same cohort [18] showed that high MUFA and PUFA energy intakes were associated with a better cognitive performance in a 8.5 –year follow-up. In the analyses of 732 participants of the EPIC Greeks cohort [36], intake of olive oil, MUFA and SFA exhibited a weak but not significant positive association with cognitive function as assessed by the MMSE, 6 to 13 years after enrolment. In this cohort, intake of PUFA was inversely associated with performance in the MMSE. Furthermore, four other studies have investigated the association between intake of omega 3 PUFA and cognition or dementia, giving conflicting results [9,15–17].

However, olive oil is more than a MUFA fat. Olive oil is a functional food which, besides having a high level of MUFA, contains other minor components with biological properties [37] such as natural antioxidants including phenolic compounds. Most antioxidant compounds have been hypothesized to have a protective effect against dementia and cognitive impairment [38]. Selective antioxidants, including E vitamins, and flavonoids, may reduce neuronal damage and death from oxidative reactions by inhibiting the generation of reactive oxygen species, lipid peroxidation, apoptosis, protein oxidation, damage to cell membranes and/or DNA and beta-amyloid toxicity or deposition [39,40]. Numerous epidemiological studies have supported these hypotheses in relation to antioxidant nutrients [41–46]. However at this stage, it is difficult to be more precise as to the mechanism by which olive oil exerts its beneficial effect on cognitive outcomes, and further studies are needed.

Our study has the following limitations. First, tests proposed in the E3C study covered a limited number of cognitive functions but the battery was prepared in order to screen for dementia cases and these tests have different metrological properties [47]. Due to ceiling effects, the BVRT is less appropriate to assess cognitive changes in subjects with very high cognitive level functioning but is rather sensitive to cognitive change in the low cognitive levels. The multiple-choice forms used in the E3C study allow assessment of visuospatial working memory - a memory system particularly vulnerable to aging [48]. The selective association between this test and olive oil consumption could be explained by its metrological properties, different from those of IST, rather than by a direct biological explanation, which is more speculative. Furthermore, even if non significant in the final model, we also observed an association between verbal fluency performance and olive oil. Absence of significant association with MMSE score may also be related to its skewed distribution.

Secondly, our dietary questionnaire is relatively short. We did not collect any information on portion size, thus excluding any quantitative approach or adjustment on caloric intake. Nevertheless, this FFQ allowed us to characterize olive oil consumers in this aged population and to control for other dietary habits which have been previously associated with dementia and cognitive decline (fish or omega 3 oil, fruits and vegetables) [9–20]. Even in FFQ more detailed, there is a large degree of reporting error in energy intake (generally under reporting) which is strongly correlated with BMI and low socio economic status. The best we could do, according to the type of data collected, was to adjust for consumption of fish, consumption of vegetables, BMI and socio economic status. Our analyses were also adjusted for other health behaviour factors such as smoking status and alcohol intake, however the lack of data on physical activities in the whole population constitutes another limitation of this study. Moreover, we cannot exclude that the beneficial effect of olive oil on cognitive decline shown in our cohort could actually be explained by the healthy dietary habits and healthy life habit behaviors associated with the regular consumption of olive oil. However the analyses adjusted for dietary intake and for socio-economic status showed that these factors had little impact on the observed associations between olive oil use and cognitive deficit or decline. Similarly it could also be argued that use of olive oil may reflect the physical and cognitive ability of the participants to prepare one's own meals. Our adjusted analyses for numerous health factors and the results obtained in our sensitivity analyses carried out after excluding incident cases of dementia make it less probable as similar associations were observed while the rates of decline were lower.

Finally, the design of our study -an observational epidemiological study- does not permit us to conclude that there is a causal link between use of olive oil and cognitive decline. However the longitudinal and multicentric design, the large sample size including more than 8000 elderly subjects from the general population, the high quality of cognitive assessment, the low rate of attrition of our cohort, and the full adjustment for the potential confounders constitute the major strengths of this report.

In conclusion, to the best of our knowledge this is the first study to show that self-reported use of olive is associated with lower odds of visual memory decline in a large general elderly population independently of other dietary intakes and after taking into account potential confounders. Even if further research is needed to confirm our finding, our results highlight the importance of olive oil in the Mediterranean diet and in its beneficial effects on health outcome.

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Figure 1

Distribution of olive oil use according to level of education

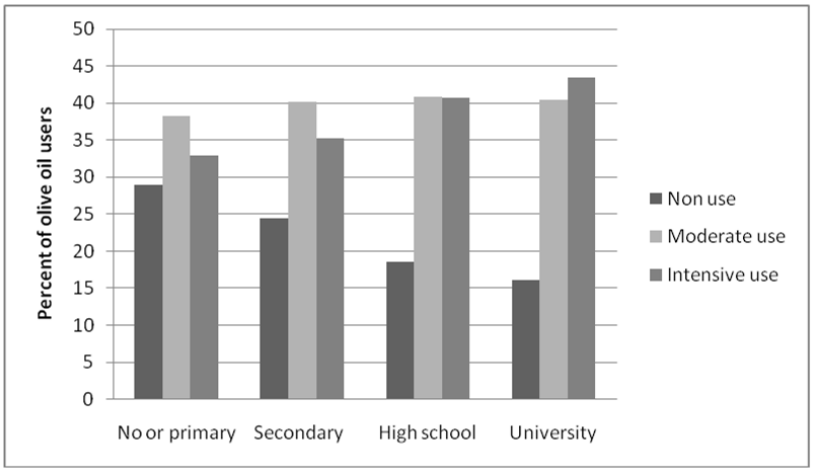

Figure 2

Cross sectional association between olive oil use and cognitive deficit at baseline: risk of cognitive deficit in olive oil users expressed by the odds-ratio value with its 95% confidence interval calculated with logistic regression model (controlling for age, sex, centre, education, income, depressive symptoms, APOE4, cardiovascular disease, hypertension, diabetes, hypercholesterolemia, BMI, smoking status and dietary intake of fruit/vegetable, omega3 oil, fish, coffee, and alcohol)

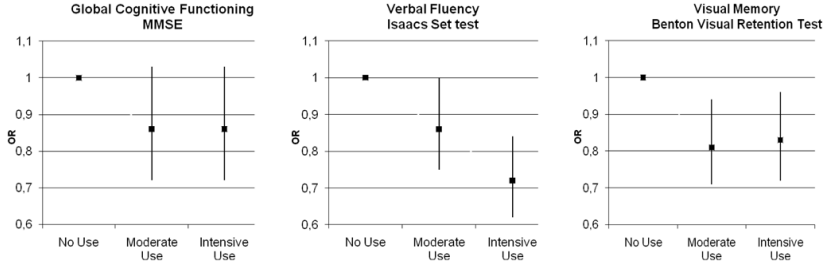

Table 1

Baseline characteristics of the 6947 participants as a function of olive oil use.

		Non use	Moderate use (cooking or dressing)	Intensive use (both cooking and dressing)	Chi2 test
	n	%	%	%	**P** *
Sex					
Men	2755	23.2	39.9	36.9	0.69
Women	4192	22.4	39.9	37.7	
Age					
65–69	1778	17.5	41.7	40.8	
70–74	2334	22.0	39.3	38.7	<0.0001
75–80	1860	25.2	39.3	35.5	
80+	975	29.2	39.1	31.7	
Education					
No or primary	1654	28.9	38.2	32.9	
Secondary	2510	24.5	40.2	35.3	<0.0001
High school	1419	18.5	40.8	40.7	
University	1364	16.1	40.5	43.4	
City					
Bordeaux	1416	33.0	38.1	28.9	
Dijon	3716	25.7	36.2	38.1	<0.0001
Montpellier	1815	8.4	48.9	42.7	
Marital status					
Married	4128	20.4	40.6	39.0	
Divorced	515	20.8	37.9	41.3	<0.0001
Widowed	1774	27.2	39.0	33.8	
Single	495	28.7	38.2	33.1	
Other	30	10.0	50.0	40.0	
Monthly income					
< 750 €	336	39.0	34.8	26.2	
750–1500 €	2122	28.6	39.0	32.4	
1500–2250 €	1976	21.9	40.2	37.9	<0.0001
>2250 €	2513	16.1	41.1	42.8	
Depressive symptoms					
< 16	5369	22.2	40.3	37.5	0.18
≥ 16	1578	24.3	38.6	37.1	
Cardiovascular Disease					
No	6336	22.5	40.0	37.5	0.45
Yes	611	24.7	39.1	36.2	
BodyMass Index					

Normal	3276	19.4	41.4	39.2	
Overweight	2758	24.4	38.5	37.1	<0.0001
Obese	913	29.1	38.9	32.0	
Diabetes					
No	6302	22.0	40.3	37.7	
Yes	645	29.0	36.1	34.9	0.0003
Hypertension					
No	3044	19.9	40.7	39.4	
Yes	3903	24.9	39.3	35.8	<0.0001
Hypercholesterolemia					
No	1794	22.1	40.0	37.9	
Yes	5153	22.9	39.9	37.2	0.79
Smoking					
Never	4230	22.7	39.9	37.4	
Former	2339	22.0	39.6	38.5	0.08
Current	378	26.7	42.1	31.2	
APOE ε4 carrier					
No	5582	22.8	40.1	37.1	0.59
Yes	1365	22.3	39.1	38.6	
Alcohol					
0	1375	29.6	39.4	31.0	
1–12 g/day	3141	20.8	39.9	39.3	<0.0001
13–36 g/day	1843	20.0	41.1	38.9	
> 36g/day	588	25.0	37.4	37.6	
Coffee					
≤ 2 cups/day	4784	23.6	39.8	36.5	
2–3 cups/day	1449	21.5	40.9	37.6	0.005
> 3 cups/day	714	18.8	38.4	42.9	
Fish					
Less than once/week	782	33.6	36.7	29.7	
Once/week	2630	28.4	39.8	31.8	<0.0001
Twice or more/week	3535	16.0	40.7	43.3	
Fruits & vegetables					
Less than twice/day	2000	29.6	37.4	33.0	
Twice/day	2549	22.3	39.6	38.1	<0.0001
3 times or more/day	2398	17.3	42.4	40.3	
Omega 3 oil					
No	6586	23.0	39.8	37.2	
Yes	361	17.5	42.1	40.4	0.05
Butter					
No	2633	21.6	40.3	38.1	

Yes	4314	23.3	39.6	37.0	0.24
Goose and duck fat					
No	6727	22.7	39.9	37.4	
Yes	220	20.0	41.4	38.6	0.63
Corn oil					
No	6762	22.7	39.6	37.7	
Yes	185	21.6	50.3	28.1	0.008
Peanuts oil					
No	5803	22.1	38.5	39.4	
Yes	1144	25.9	46.9	27.2	<0.0001
Sunflower oil					
No	3665	16.5	35.8	47.7	
Yes	3282	29.5	44.5	26.0	<0.0001
MMSE baseline					
≥ 26	5951	21.8	40.2	38.0	0.0002
< 26	970	27.6	38.5	33.9	
IST 30 baseline**					
> 40	5246	20.4	39.9	39.7	<0.0001
≤ 40	1624	29.9	39.9	30.2	
BVRT baseline**					
> 10	4973	20.2	41.1	38.7	<0.0001
≤ 10	1893	28.8	37.3	33.9	

* P value are given for the global chi2 test of heterogeneity. We have examined all comparisons between moderate use vs. no use and intensive use vs. no use.
For variables for which heterogeneity test was significant at p<0.05, all 2 by 2 comparisons were significant except when comparing moderate use vs. no use for: coffee consumption (p=0.11), corn oil use (p=0.13), peanuts oil (p=0.63).

** Cut-off corresponding to the first quartile of the sample distribution
MMSE= Mini Mental State Examination (global cognitive functioning)
IST= Isaacs Set Test (verbal fluency)
BVRT= Benton Visual Retention Test (visual memory)

Table 2

Longitudinal association between olive oil consumption and cognitive decline

	Cognitive decline		Model 0		Model 1		Model 2	
	%	p	OR(95% CI)	p	OR(95% CI)	p	OR(95% CI)	p
Global cognitive functioning		0.37						
No use	14.9		1		1		1	
Moderate use	14.1		0.90 (0.74–1.08)	0.24	0.91 (0.76–1.10)	0.32	0.94 (0.78–1.13)	0.50
Intensive Use	13.3		0.90(0.74–1.09)	0.27	0.91 (0.75–1.10)	0.34	0.95 (0.78–1.15)	0.58
Verbal fluency		0.30						
No use	16.6		1		1		1	
Moderate use	15.7		0.93 (0.78–1.12)	0.47	0.95 (0.79–1.14)	0.55	0.96 (0.80–1.16)	0.69
Intensive Use	14.8		0.83 (0.68–0.99)	0.04	0.83 (0.69–1.00)	0.05	0.85 (0.70–1.03)	0.10
Visual memory		0.01						
No use	21.4		1		1		1	
Moderate use	19.1		0.88 (0.75–1.05)	0.15	0.90 (0.76–1.07)	0.25	0.91 (0.77–1.09)	0.30
Intensive Use	17.8		0.80 (0.68–0.96)	0.01	0.82 (0.69–0.97)	0.02	0.83 (0.69–0.99)	0.04

Model 0: adjusted on age, sex, centre, education, income and baseline cognitive score
Model 1: Model0 **+**, depressive symptoms, APOE4, cardiovascular disease, hypertension, diabetes, hypercholesterolemia, BMI
Model 2: Model 1 **+** smoking status and dietary intake of fruit/vegetable, omega3 oil, fish, coffee, and alcohol