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Refined carbohydrate-rich diet is associated with long-term risk of dementia and Alzheimer's disease in apolipoprotein E ϵ 4 allele carriers

Mélissa Gentreau^a, Virginie Chuy^b, Catherine Féart^b, Cécilia Samieri^b, Karen Ritchie^a, Michel Raymond^c, Claire Berticat^{c#}, Sylvaine Artero^{a##*}

¹*^a Neuropsychiat Rech Epidemiol & Clin, Univ Montpellier, INSERM, Montpellier, France*

²*^b Bordeaux Population Health Research Center, Univ Bordeaux, INSERM, Bordeaux, France*

^c*ISEM, Univ Montpellier, CNRS, EPHE, IRD, Montpellier, France.*

These authors contributed equally to this work.

* Corresponding author. Sylvaine Artero, 39 av Charles Flahault BP 34493; 34093 Montpellier cedex 5

Tel.: 0499614568

E-mail address: sylvaine.artero@inserm.fr

Abstract

INTRODUCTION: In animal models, refined carbohydrates (RF) worsen Alzheimer's disease (AD). However, the long-term effects of high RF intake on the risk of dementia and AD are poorly described in epidemiological studies. Moreover, the interaction between RF and apolipoprotein E ϵ 4 allele (*APOE- ϵ 4*) is unknown. Our study investigated whether RF-rich diets are associated with the risk of dementia and AD.

METHODS: The glycemic load was quantified in 2,777 elderly participants from the French Three-City Study to estimate RF intake. Then, the association between glycemic load and risk of dementia and AD, and the interaction with *APOE- ϵ 4* over a 12-year period were assessed using proportional hazards models.

RESULTS: After adjustment for potential confounders, high afternoon-snack glycemic load was associated with increased dementia and AD risk in *APOE-ε4* carriers (HR = 1.27 [1.03-1.56]).

DISCUSSION: This study highlights that RF-rich diets are a risk factor for dementia and AD in *APOE-ε4* carriers.

Keywords: Dementia, Alzheimer's disease, Apolipoprotein E ε4, glycemic load, Refined carbohydrate, Sugar, Diet, Cohort study

1. Introduction

According to the World Health Organization (WHO), dementia will affect more than 152 million people by 2050 [1]. Currently no effective treatment is available to cure or slow down dementia progression. After the repeated failure of clinical trials, now the most promising research focuses on preventing dementia. Therefore, it is urgent to identify modifiable factors that could be targeted in interventions to prevent dementia and to promote better brain health in aging populations. Among these modifiable factors, nutrition has emerged as an important issue [2], particularly the steady increase in the consumption of refined carbohydrates [3]. Refined carbohydrates are carbohydrates that are rapidly absorbed into the bloodstream, and include starches and sugars (sucrose, glucose-fructose syrup). The glycemic and insulinemic responses progressively increase with more processed carbohydrates. Moreover, some meals are typically high in refined carbohydrates (i.e., breakfast and afternoon snack) [4], suggesting that they are at greater risk of inducing large glycemic and insulinemic responses.

In mouse models of Alzheimer's disease (AD), high sugar diet worsens AD pathophysiology, notably by causing memory impairment and increasing amyloid

beta deposits. These studies also demonstrated that high-sugar diet alters brain insulin signalling and leads to insulin resistance [5,6]. This suggests that diets rich in refined carbohydrates could promote dementia and AD through insulin resistance [7]. However, insulin resistance and refined carbohydrate-rich diet are important risk factors of type 2 diabetes (T2D), therefore T2D could be a confounder in the relationship between refined carbohydrate-rich diet and dementia.

To date the direct association between refined carbohydrate-rich diet and the risk of dementia or cognitive decline has not been adequately investigated in epidemiological studies [8,9], as they have been mostly cross-sectional studies with small sample sizes. They showed that refined carbohydrates consumption is associated with higher amyloid deposits [10], lower entorhinal cortical thickness [11], and poorer cognitive performance [12]. The few existing longitudinal studies have yielded inconsistent results [13–15]. Moreover, wide range of methods have been used to assess carbohydrate consumption: self-reports [13], adherence to a dietary pattern [10], percentages of calories from carbohydrates [11], glycemic index and/or glycemic load [12,14,15].

Previous epidemiological studies also suggest that a refined carbohydrate-rich diet may interact with the apolipoprotein E ϵ 4 allele (*APOE- ϵ 4*), the principal genetic risk factor of AD and dementia. In animal studies, *APOE- ϵ 4* carriers are more likely to develop insulin resistance [16], and this could be exacerbated by consumption of refined carbohydrates [5,6]. Nevertheless, the potential interaction between refined carbohydrate-rich diet and *APOE- ϵ 4* on the risk of dementia has not been studied in humans.

The objective of this study was to determine whether high refined carbohydrate intake, estimated by quantifying the glycemic load, is associated

with the risk of dementia in a large population-based prospective cohort study with a 12-year follow-up (the Three-City Study). The present study addressed four questions: (1) Is refined-carbohydrate-rich diet associated with dementia? (2) Are some meals more at risk than others? (3) Does refined carbohydrate-rich diet interact with *APOE-ε4*? (4) Is the association independent of T2D?

2. Methods

2.1 Study participants

The Three-City Study is a French population-based cohort study on 9,294 people, aged 65 years and over who were randomly selected between 1999 and 2000 from the electoral roll of three French cities: Bordeaux, Dijon, and Montpellier. A detailed description of the Three-City Study has been provided elsewhere [17]. Participants had face-to-face interviews with trained nurses and psychologists at baseline, and at 2, 4, 7, 10, 12 and 15-years follow-up (FU) (Fig. 1). Questionnaires were used to collect data on socio-demographic and lifestyle characteristics, education level, self-reported chronic diseases, depressive symptoms, and functional status. In addition, participants underwent a comprehensive evaluation of cognitive and physical functions. The present study focused on a subsample of participants from Bordeaux ($n = 1755$) and Montpellier ($n = 1690$) who filled in the food frequency questionnaire (FFQ) at the first and second follow-up (i.e., 2 and 4 years after baseline), respectively (Fig.1). Participants with prevalent dementia at the time of FFQ completion were excluded. A flow chart describes the participants' selection (Fig. 2). At the end of the study, the mortality rate was 26.9 % and the rate of lost participants in the FU was 21.0%. The Ethical Committee of the University Hospital of Bicêtre

(France) approved the study protocol, and all participants signed an informed consent.

2.2 Dietary data

2.2.1 Food Frequency Questionnaire

Dietary data were collected using a semi-quantitative, 148-item FFQ at 1-FU for Bordeaux and 2-FU for Montpellier (Fig. 1). The FFQ was divided into: breakfast, lunch, dinner, and snacks between meals (extract from the FFQ in Supplementary Table 1). Reported frequencies were transformed into discrete variables as follows: 0 for never or less than once a month, 0.25 for once a month, 0.5 for twice a month, 0.75 for three times a month, 1 to 7 for one to seven times per week [18]. Discrete variables were expressed in servings per week.

2.2.2 24-h dietary recall interview

A 24-h dietary recall interview was performed at the Bordeaux center at 1-FU by trained dietitians. For each item, seven serving sizes were available. Concordance between FFQ and 24-h dietary recall was previously checked for fatty acids [19]. These data were only used in sensitivity analyses.

2.2.3 glycaemic load

The glycaemic index values of FFQ items were obtained from the International Table of Glycaemic Index [20] and internet updates (www.glycaemicindex.com), using glucose as the reference. The glycaemic index compares the rate of glucose release by measuring the 2h postprandial glycaemia after consumption of a food portion containing 50 g of available carbohydrates. glycaemic load (GL) reflects both the carbohydrate quantity and quality [20,21]. Compared with low-GL diets, high-GL diets elicit larger glycaemic and insulinemic responses [9,12,20]. For each FFQ item (i.e., food/beverage categories), GL was calculated by multiplying the

glycemic index by the amount of available carbohydrates (g) per serving, divided by 100 [22]. Foods with low carbohydrate content (e.g., meat, fish, fats) were not assigned any GL value [23]. Then, the GL for each item was multiplied by the frequency of consumption/week reported by each participant. Finally, the sum of this last value for all the items consumed during a meal gave the total GL for breakfast, lunch, afternoon snack (“goûter” in French, corresponding to a snack between lunch and dinner), and dinner. The GL from the 24-h dietary recall was estimated using precise food item data and gathered by meal. The daily GL was either the sum of all the FFQ items or the 24-h dietary recall. The total GL values for breakfast, lunch, afternoon snack, and dinner from the FFQ and the 24-h dietary recall were significantly correlated in the Bordeaux subsample (range: 0.30 to 0.57). Precise estimation of carbohydrate content was not possible with this FFQ.

2.2.4 *Energy intake*

Energy intakes for the corresponding items in the FFQ were obtained from the Anses-Ciquial database (www.anses.ciquial.fr). The energy intake per serving of each item was multiplied by the reported frequencies. Then, the sum of the energy intake for the items consumed at each eating occasion gave the energy intake of each meal. The energy intakes from the 24-h dietary recall were derived as previously described [19]. Although the FFQ underestimated the energy intake, the energy intakes for breakfast, lunch, afternoon snack, and dinner from the FFQ and the 24-h dietary recall in the Bordeaux subsample were significantly correlated (range: 0.20 to 0.53)

2.2.5 *Mediterranean diet-like score*

To take into account the diet quality, a Mediterranean diet-like score was calculated. Items were grouped according to the nine components of the Mediterranean diet score [24,25]. For fruits, vegetables, legumes, cereals, and

fish, 1 point was assigned when the participant's consumption was above the median, 0 otherwise. For meat and dairy, 1 point was assigned when the participant's consumption was below the median, 0 otherwise. For alcohol, 1 point was assigned when consumption was below 20 g of ethanol per day for men and 5.7 g for women (i.e., low-to-moderate alcohol consumption in this population). For the ratio of monounsaturated fatty acids to saturated fatty acids, 1 point was assigned when the ratio was above the sex-specific median, 0 otherwise. The total Mediterranean diet-like score ranged from 0 (lowest adherence) to 9 (highest adherence).

2.3 Diagnosis of dementia

The diagnosis of dementia and its classification was made at each follow-up by the Three-City Study local clinical investigators, following standardized procedures. Then, an independent committee of neurologists examined all potential cases of dementia to obtain a consensus on the diagnosis and aetiology based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [26]. Cases of dementia, including AD, were classified according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria [27], and cases of mixed/vascular dementia according to the National Institute of Neurological Disorders and Stroke/Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria [28]. Mixed dementia was defined as an AD-type cognitive profile with either cerebrovascular lesions on brain imaging, or a documented history of stroke and presence of prominent executive function deficits, attested by the Trail Making Test [29].

2.4 Covariates

Education level was defined as no school, primary school, high school, or graduated level. The Mini Mental State Examination (MMSE) [30] was used as an index of global cognitive performance. Body mass index (BMI) was calculated as weight (kg)/height² (m). Hypertension was defined by systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg, or use of antihypertensive drugs [31]. History of head trauma and stroke was established using standardized questions. Cardiovascular history included history of myocardial infarction, coronary surgery, coronary angioplasty, and arterial surgery of the legs for arteritis. Hypercholesterolemia was defined as total cholesterol ≥ 6.2 mmol.L⁻¹. T2D was defined as treated diabetes, fasting glycemia > 7 mmol.L⁻¹, and additionally self-reported. Apolipoprotein E genotyping was described elsewhere [32]. *APOE*- $\epsilon 4$ carriers had at least one $\epsilon 4$ allele. Information was also obtained on the subjectively evaluated health and smoking status (never, past, or current). Depressive symptomatology was evaluated with the Center for Epidemiological Studies-Depression (CES-D) scale [33], using the recommended French cut-off scores at 17 and 23 points for clinically relevant depressive symptom burden in older men and women, respectively [34]. As physical activity was assessed in a slightly different manner in the two centers [35], a common binary variable was defined (none or low/regular).

2.5 Data analysis

2.5.1 Covariates selection

First, the main confounding factors of dementia and potential confounding factors related to carbohydrates were pre-selected. For the outcome-related covariates (dementia) proportional hazard models adjusted for center, age, sex and education were performed. For exposure-related_covariates (daily GL)

Pearson correlations (for continuous variables) or ANOVA (for categorical variables) were used. In both cases, covariates with a P value < .10 were selected.

2.5.2 *Main analyses*

Proportional hazards models were used to evaluate the association between the GL and the risk of all-cause dementia over the 11-13-year follow-up (mean follow-up = 11.4 ± 2 years), in five separated analyses (i.e. daily, breakfast, lunch, afternoon snack, dinner). This modelling considers the time of dementia onset and the participants out of the study (i.e. death, loss of follow-up). In Model 1, analyses were adjusted for center, age (at the time of the FFQ), sex, education, *APOE-ε4* carrier status, BMI, T2D, hypertension, cardiovascular history, stroke, hypercholesterolemia, head trauma, good subjective health, and tobacco (i.e., the main confounding factors of dementia) [36]. In Model 2, Mediterranean diet-like score and physical activity were also added relative to the Model 1, due to the high percentage of missing values (6.7% for the Mediterranean diet-like score and 14.3% for physical activity). In Model 3, incomplete variables were imputed (see below) and analyses were adjusted for the same variables as in Model 2. The interaction between GL and *APOE-ε4* was tested and was kept in the model when significant. The proportional hazards assumption was tested with the Schöenfeld residuals method. Kaplan-Meier survival curves were used to graphically illustrate survival findings.

2.5.3 *Imputation of missing values*

The percentage of missing values across covariates varied between 0 and 14.3%. To minimize the loss of power and selection bias, incomplete variables were imputed using the *mice* package [37]. To include a large number of related predictor variables without encountering problems due to collinearity [38], we used random forest method. Eight multiply imputed datasets were created and

analyzed. The parameters of interest were estimated in each imputed dataset separately, and combined using Rubin's rules. The combined results of the imputed datasets are presented in Model 3.

2.5.4 Sensitivity analyses

First, the main analyses concerning participants from Bordeaux were replicated using the GL values estimated from the 24-h dietary recall results. Then, participants (both centers) with T2D were excluded to confirm that GL effect was not mediated by T2D (T2D participants had reduced GL values). Finally, analyses were restricted to AD by excluding participants (both centers) with incident mixed and vascular dementia from the main analyses.

Statistical analyses were performed with the R 3.4.3 software (www.r-project.org). Two-sided P values were used with $\alpha = .05$ as threshold for statistical significance.

3. Results

A total of 2,777 participants (n=1,376 from Montpellier and n=1,401 from Bordeaux) were included in the analyses (Table 1, Supplementary Table 2). At the time of the FFQ, the participants' mean age was 75.9 years, 61.1% were women, and 10.1% had T2D. During a mean follow-up time of 11.4 years (SD = 2.0 years), 350 participants developed dementia: 260 cases of AD, 49 cases of mixed dementia, and 41 cases of vascular dementia were identified.

3.1 *The statistical interaction between glycemc load and APOE-ε4 carrier status is associated with the risk of dementia*

We asked whether the GL, as an estimation of refined carbohydrate consumption, was associated with the risk of dementia during the 11.4 years of follow-up (Table 2). We did not find any direct association between dementia and the daily GL or GL value of breakfast, lunch, afternoon snack, and dinner. However, the interaction between afternoon-snack GL and *APOE*- ϵ 4 carrier status was significantly associated with the dementia risk. *APOE*- ϵ 4 carrier status was also associated with the dementia risk. After adjustments for Mediterranean-diet-like score and physical activity (Model 2), the interaction remained significant. Significant covariates were *APOE*- ϵ 4 carrier status, age, T2D and history of head trauma as risk factors and living in Montpellier as protective factor (Fig. 3). Multiple imputations (Model 3) did not change these results showing that the risk of dementia was higher in *APOE*- ϵ 4 carriers who consumed afternoon snacks with high GL value. To quantify this association, we stratified by *APOE*- ϵ 4 (Supplementary Figure 1, Supplementary Figure 2). In *APOE*- ϵ 4 carriers, hazard ratio for a 10-point increase in the GL value per day was 2.06 [1.07-4.0]. Finally, in categorical analyses the interaction between the higher tercile of the afternoon-snack GL and *APOE*- ϵ 4 carrier status was significantly associated with the dementia risk (Supplementary Table 3). Kaplan-Meyer survival curves clearly illustrated it (Supplementary Figure 3).

3.2 *Sensitivity analyses*

By estimating the GL on the basis of the FFQ results, we hypothesized that participants consumed standard serving sizes, leading to potential measurement errors. To evaluate this potential bias, we ran a sensitivity analysis in the Bordeaux subsample using the GL values estimated from the 24-h dietary recall (Table 3). Proportional hazards models confirmed that the interaction between afternoon-snack GL and *APOE*- ϵ 4 carrier status was associated with dementia. Hazard ratios estimated from the 24-h dietary recall were comparable to those

calculated using the FFQ data. These analyses validated our results obtained with the GL values estimated from the FFQ. Moreover, results were not modified by excluding participants with T2D from the analyses (Supplementary Table 4). Finally, we showed that the interaction between afternoon-snack GL and *APOE-ε4* carrier status was significantly associated with the risk of AD by excluding participants with incident mixed and vascular dementia (Supplementary Table 5).

4. Discussion

In this 12-year follow-up study, we found that higher afternoon-snack GL was associated with an increased risk of dementia and AD in *APOE-ε4* carriers using two methods for GL evaluation. This result was independent of energy intake, Mediterranean-like diet, physical activity, and remained significant after exclusion of participants with T2D. The daily GL and GL values of breakfast, lunch and dinner were not associated with the risk of dementia and AD.

Few previous studies have explored the association between refined carbohydrate intake and dementia or AD. In a cross-sectional analysis, sugar-sweetened beverages were associated with several markers of preclinical AD, such as low total brain volume, and poor Immediate and Delayed Logical Memory scores [39]. Similarly, in another study (n=208 elderly participants), diet with high GL was associated with poor cognitive performance [12]. The only study on the association between GL and AD did not find any significant association [15]. As in our study, the authors tested the daily GL, but not GL by meal. They did not check for an interaction with *APOE-ε4* and had a shorter follow-up (6.3 years). In the Framingham Heart Study (10-year follow-up) no association was found between sugar-sweetened beverages and dementia [40]. Conversely, in the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study, sugar intake

reduction (self-reported) in midlife was associated with lower dementia risk over 16.8 years [13]. Other studies reported differences according to the *APOE-ε4* carrier status. Specifically, the association between T2D and AD was stronger among *APOE-ε4* carriers (3.7 times higher) [41]. In *APOE-ε4* carriers, high midlife glycemia was associated with more serious AD neuropathology [42]. Conversely, Schrijvers *et al.*, (2010) did not find any significant effect of the interaction between *APOE-ε4* carriers and insulin metabolism on AD risk [43].

The statistical interaction between *APOE-ε4* carrier and afternoon-snack GL on the risk of dementia could be explained in three ways. First, afternoon snacks with high GL could induce oxidative stress, a favourable environment for insulin resistance. Afternoon snacks tend to have high GL because they are usually richer in refined carbohydrates, especially sweets, cereal bars, biscuits, and sodas [4] (Supplementary Table 6, Supplementary Fig 4). Snacks are digested more rapidly than full meals because of their lower content in fat and fibre. Thus, post-prandial glycemia quickly increases and induces a high peak in insulin secretion. This chronically repeated high and transitory insulin peaks could promote insulin resistance through oxidative stress and inflammation [44,45] (glucose toxicity hypothesis). Second, *APOE-ε4* carriers are more likely to develop insulin resistance. As *APOE-ε4* carriers have lower antioxidant activity than *APOE-ε4* non-carriers [46], they are less resistant to oxidative stress. Evidence from several studies suggests that *APOE-ε4* carriers are less sensitive to insulin. Animal experiments provided a molecular explanation of this observation. In mice that express human *APOE-ε4*, apoE4 impairs insulin signalling in cortex and hippocampus in an age-dependent manner [16]. Moreover, in these mice, the transcription factor peroxisome proliferator-activated receptor gamma (PPAR-γ), which increases insulin sensitivity, is downregulated [47,48], and glucose

metabolism in brain is decreased. The authors found that this lower glucose metabolism was caused by impaired glucose uptake, glycolytic activity, and mitochondrial respiration. These results are in agreement with epidemiological studies showing that *APOE-ε4* carriers have lower brain glucose metabolism (measured by ¹⁸F-fluorodeoxyglucose positron-emission tomography) [49,50]. Third, the association between insulin resistance and dementia risk is stronger in *APOE-ε4* carriers. In the Uppsala Longitudinal Study of Adult Men, high fasting serum insulin and Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) index were associated with dementia or cognitive impairment over 32 years [51]. The association was stronger in *APOE-ε4* carriers. We could hypothesize that high intake of refined carbohydrates at afternoon-snack time induces insulin resistance that in turn promotes dementia development. Alternatively, perhaps *APOE-ε4* carriers spontaneously consume more refined carbohydrates to compensate for the lower glucose metabolism induced by apoE4. However, in our sample carbohydrate-based food groups were not different between *APOE-ε4* carriers and non-carriers (data not shown).

On the other hand, the estimated GL values for breakfast, lunch and dinner might not reflect the real GL values resulting from the digestion of all food together (i.e., carbohydrates with vegetables, meat, fish, and fat). During meals, carbohydrates are rarely ingested alone, and their degradation and absorption rates during digestion are modified by the other macronutrients. For example, adding fat and/or protein components to a high glycemic index meal decreases the glycemic response [52]. Dietary fibres have a similar effect [53]. The order of food macronutrient intake also changes the glycemic and insulinemic responses. Indeed, higher postprandial glycemic and insulinemic responses are observed when high glycemic index carbohydrates (e.g. rice) are eaten first and then vegetables and meat compared with eating all these foods together [54].

The major strengths of our study are the prospective population-based design, the large number of participants, and the long follow-up period. Data from the 24-h dietary recall (Bordeaux subsample) validated the results obtained with the FFQ. Moreover, we adjusted for numerous confounding factors. Specifically, our results are independent from, energy intake, BMI, diet quality, physical activity, T2D and also from a possible protective effect of Mediterranean lifestyle (living in the Montpellier center). However, our study presents some limitations. First, we did not repeat the FFQ during the follow-up. Hence, we could not determine the participants' exposure duration to the actual diet and we do not know whether participants changed their dietary habits during the follow-up. Second, the dietary habits, assessed 12 years ago, could have already reflected changes due to the first symptoms of dementia pathology (protopathic bias). This might have overestimated the association between afternoon-snack GL and dementia risk in *APOE*- ϵ 4 carriers. Third, we did not have access to fasting serum insulin data to calculate the HOMA-IR index and to test whether there is an interaction between *APOE*- ϵ 4 carriers and insulin resistance. Thus, we could not verify whether insulin resistance promotes dementia.

In our prospective cohort study, afternoon snacks rich in refined carbohydrates were associated with dementia risk in *APOE*- ϵ 4 carriers. These results pave the way to new prevention strategies. However, large-scale studies in different populations and using a homogenous methodology are required to replicate this observation. Moreover, the statistical interaction between *APOE*- ϵ 4 status and refined carbohydrate-rich diet should be assessed in future studies. More investigations are needed to explain the mechanisms underlying the role of refined carbohydrate intake, glycemic response and *APOE*- ϵ 4 in dementia pathophysiology.

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Supplementary data

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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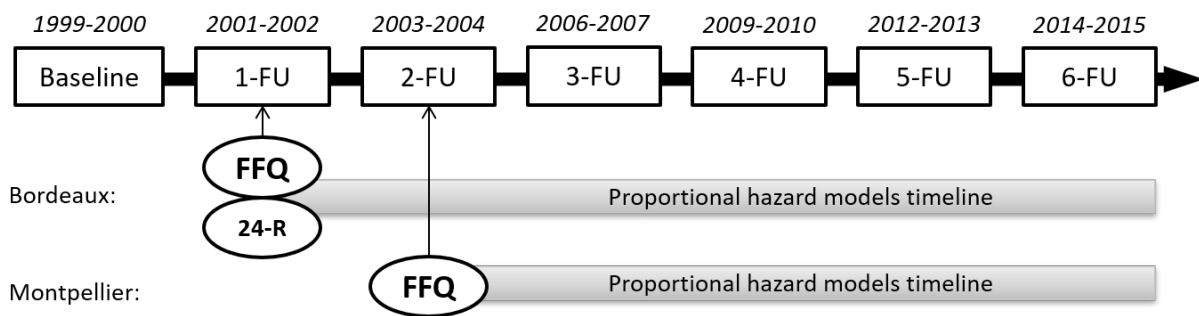


Fig. 1. Time frame of the Three-City Study at the Bordeaux and Montpellier centers. Diagnosis of dementia is made at each follow-up visit (FU). The food frequency questionnaire (FFQ) was completed by participants at 1-FU in Bordeaux and at 2-FU in Montpellier. The 24-h dietary recall (24-R) was only completed by participants at 1-FU in Bordeaux.

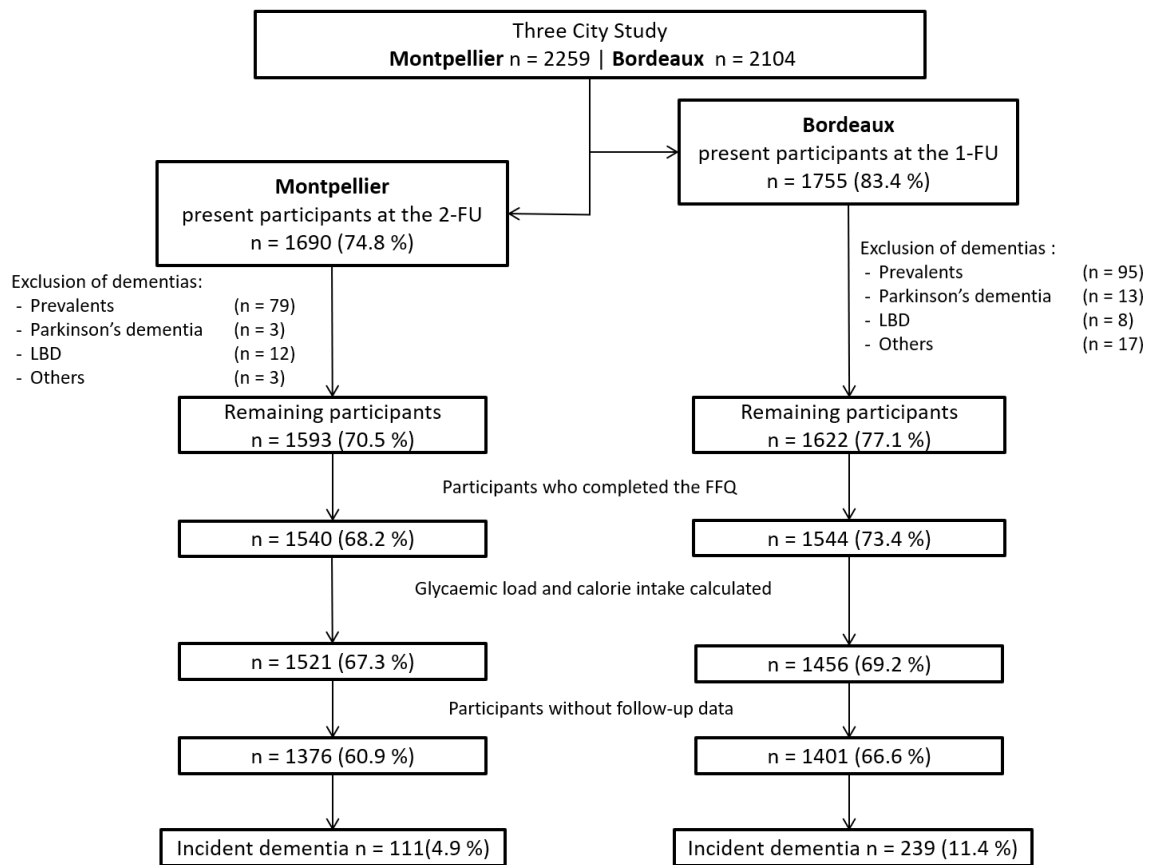


Fig. 2. Flow chart of the study sample from the Bordeaux and Montpellier centers of the Three-City Study. Abbreviations: FFQ, Food frequency questionnaire; FU, follow-up; LBD, Lewy Body Dementia.

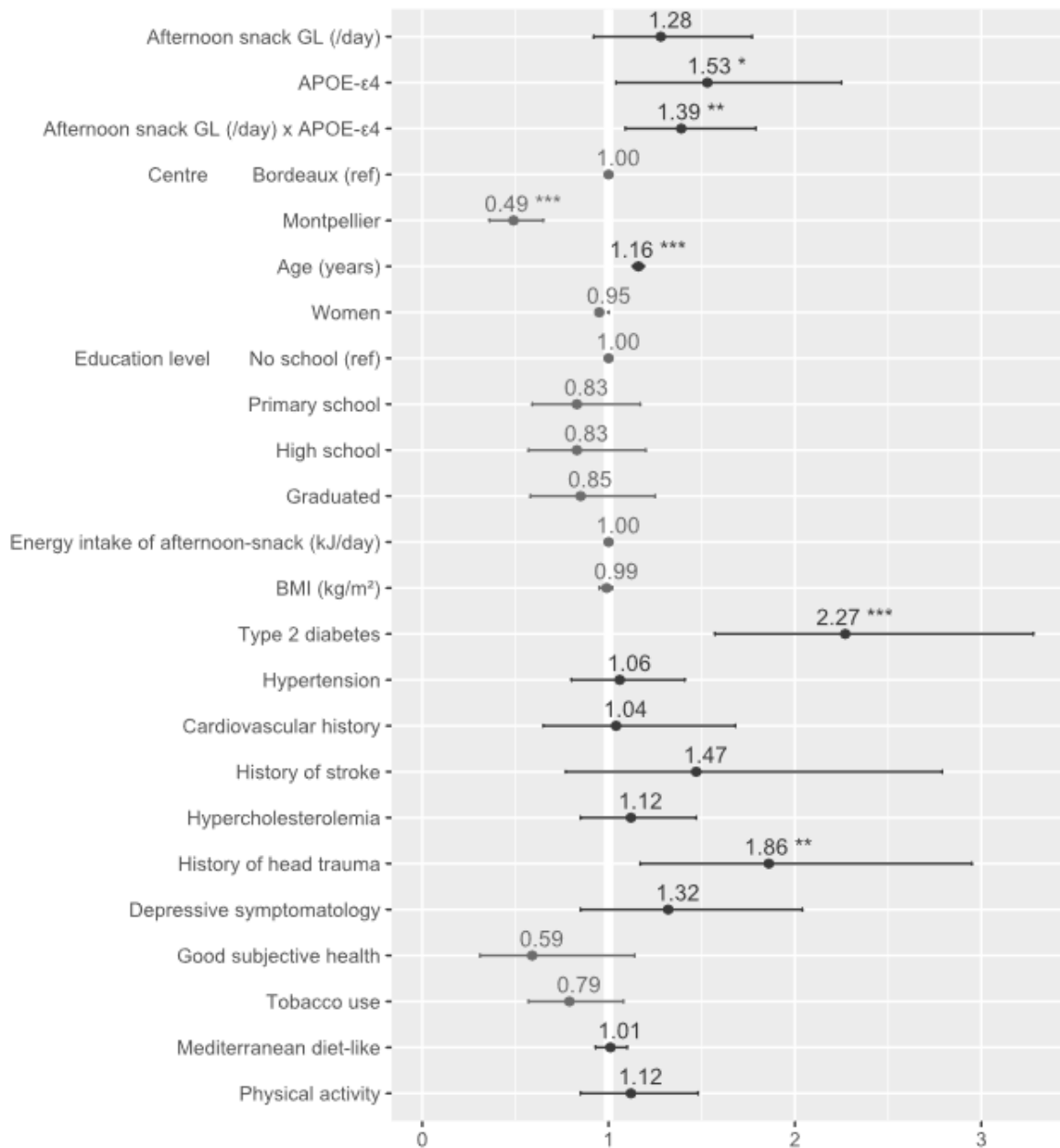


Fig. 3. Estimated hazard ratios of all covariates from Model 2 (n = 2,145). The hazard ratio of the afternoon-snack GL is expressed as a 10-point increase of the GL value per day that is equivalent to eating an additional 30 g of French baguette at each corresponding meal. Abbreviations: APOE-ε4, apolipoprotein E ε4 allele; BMI, body mass index; GL, glycemic load.* P value < .05; ** P value < .01; *** P value < .001.

Table 1 Characteristics of the study population

| Characteristics | Mean (SD) or n (%) | Range | Missing values (%) |
|-------------------------------------|--------------------|--------------|--------------------|
| Montpellier center | 1376 (49.6) | | |
| Age (years) | 75.9 (4.9) | 68 - 96 | |
| Women | 1696 (61.1) | | |
| Education level | | | |
| No school | 737 (26.5) | | |
| Primary school | 784 (28.2) | | |
| High school | 635 (22.9) | | |
| Graduated | 614 (22.1) | | |
| MMSE (IQR) | 28 (27-29) | 19 - 30 | |
| <i>APOE</i> - ϵ 4 carriers | 482 (17.5) | | 5.3 |
| BMI (kg/m ²) | 25.7 (3.9) | 13.59 - | |
| Type 2 diabetes | 281 (10.1) | | |
| Hypertension | 1676 (60.4) | | |
| Cardiovascular history | 307 (11.1) | | |
| History of stroke | 116 (4.2) | | |
| Hypercholesterolemia | 1536 (55.3) | | 3.1 |
| History of head trauma | 176 (6.34) | | |
| Depressive | 220 (7.92) | | |
| Good subjective health | 2657 (95.7) | | |
| Tobacco use (current or | 1066 (38.4) | | |
| Mediterranean diet-like | 4.7 (1.6) | 0 - 9 | 6.7 |
| Physical activity | 894 (32.19) | | 14.3 |
| glycemic load (/day) | 108.3 (34.3) | 10.6 - 323.6 | |
| Energy intake (kJ/day) | 4851 (1537) | 1311 - | |

*evaluated with the Center for Epidemiological Studies-Depression scale. Abbreviations: *APOE*- ϵ 4, apolipoprotein E ϵ 4 allele; BMI, body mass index; MMSE, Mini Mental State Examination; SD, standard deviation.

Table 2. Association between glycemic load and risk of dementia over 11.4 ± 2 years of follow-up.

| Exposure | Model 1 n = 2,572 | | Model 2 n = 2,145 | | Model 3 n = 2,777 | |
|---------------------------------|----------------------|-------------|----------------------|-------------|----------------------|-------------|
| | HR*(CI) | P value | HR*(CI) | P value | HR*(CI) | P value |
| Daily | | | | | | |
| GL | 0.99 (0.91-1.08) | .86 | 1.00 (0.91-1.11) | .97 | 1.01 (0.94-1.10) | .73 |
| <i>APOE</i> - ϵ 4 | 1.12 (0.44-2.90) | .81 | 1.14 (0.38-3.40) | .82 | 1.32 (0.53-3.29) | .56 |
| GL x <i>APOE</i> - ϵ 4 | 1.05 (0.97-1.14) | .21 | 1.05 (0.96-1.16) | .28 | 1.04 (0.96-1.13) | .32 |
| Breakfast | | | | | | |
| GL | 0.97 (0.81-1.15) | .72 | 0.99 (0.80-1.21) | .90 | 1.03 (0.87-1.21) | .75 |
| <i>APOE</i> - ϵ 4 | 1.46 (0.79-2.70) | .23 | 1.80 (0.89-3.64) | .10 | 1.58 (0.88-2.85) | .12 |
| GL x <i>APOE</i> - ϵ 4 | 1.13 (0.92-1.40) | .25 | 1.05 (0.82-1.34) | .72 | 1.10 (0.90-1.35) | .34 |
| Lunch | | | | | | |
| GL | 0.91 (0.72-1.15) | .43 | 0.91 (0.69-1.21) | .53 | 0.99 (0.80-1.24) | .96 |
| <i>APOE</i> - ϵ 4 | 2.07 (0.82-5.2) | .12 | 2.65 (0.90-7.84) | .078 | 2.16 (0.88-5.29) | .093 |
| CG x <i>APOE</i> - ϵ 4 | 0.99 (0.76-1.29) | .96 | 0.92 (0.67-1.27) | .62 | 0.98 (0.76-1.27) | .91 |
| Afternoon snack | | | | | | |
| GL | 1.18 (0.89-1.55) | .24 | 1.28 (0.92-1.77) | .14 | 1.13 (0.87-1.46) | .36 |
| <i>APOE</i> - ϵ 4 | 1.59 (1.14-2.22) | .007 | 1.53 (1.04-2.25) | .03 | 1.65 (1.20-2.28) | .002 |
| GL x <i>APOE</i> - ϵ 4 | 1.31 (1.05-1.63) | .015 | 1.39 (1.09-1.79) | .009 | 1.27 (1.03-1.57) | .027 |

| | | | | | | | |
|---------------------------------|------------------|------|------------------|------|------------------|------|--|
| Dinner | | | | | | | |
| GL | 0.92 (0.74-1.13) | .42 | 0.94 (0.73-1.22) | .65 | 0.88 (0.72-1.09) | .25 | |
| <i>APOE</i> - ϵ 4 | 2.73 (1.25-5.96) | .012 | 2.65 (1.03-6.86) | .044 | 2.84 (1.33-6.08) | .007 | |
| GL x <i>APOE</i> - ϵ 4 | 0.91 (0.73-1.14) | .42 | 0.92 (0.71-1.20) | .56 | 0.91 (0.73-1.12) | .36 | |

Abbreviations: *APOE*- ϵ 4, Apolipoprotein E ϵ 4 allele; CI, confidence interval; GL, glycemic load; HR, hazard ratio.

NOTE. Proportional hazard models. Model 1 was adjusted for inclusion center, age, sex, education level, energy intake, *APOE*- ϵ 4 status, BMI, type 2 diabetes, hypertension, cardiovascular history, history of stroke, hypercholesterolemia, history of head trauma, depressive symptomatology, subjective health, and tobacco. Model 2 included additional adjustments for Mediterranean diet-like score and physical activity. Model 3 is Model 2 with multiple imputations

* HR for a 10-point increase in the GL value per day that is equivalent to eating an additional 30 g of a French baguette at each corresponding meal.

Table 3. Association between the glycemic load, estimated from the 24-h dietary recall interview (Bordeaux center), and the risk of dementia during 13 years of follow-up.

| Exposure | Model 1 n = 1,229 | | Model 2 n = 954 | |
|---------------------------------|----------------------|----------------|--------------------|----------------|
| | HR*(CI) | <i>P</i> value | HR*(CI) | <i>P</i> value |
| Daily | | | | |
| GL | 1.01 (0.96-1.07) | .62 | 1.01 (0.94-1.07) | .82 |
| <i>APOE</i> - ϵ 4 | 1.59 (0.58-4.31) | .36 | 1.45 (0.45-4.65) | .53 |
| GL x <i>APOE</i> - ϵ 4 | 1.00 (0.92-1.10) | .95 | 1.01 (0.90-1.12) | .93 |
| Breakfast | | | | |
| GL | 1.02 (0.85-1.23) | .85 | 1.04 (0.84-1.29) | .73 |
| <i>APOE</i> - ϵ 4 | 1.61 (0.87-2.97) | .13 | 1.71 (0.82-3.54) | .15 |
| GL x <i>APOE</i> - ϵ 4 | 1.01 (0.82-1.23) | .95 | 0.95 (0.74-1.22) | .69 |

| | | | | | |
|---------------------|------------------|-------------|------------------|-------------|--|
| Lunch | | | | | |
| GL | 1.00 (0.9-1.11) | .94 | 1.01 (0.90-1.14) | .85 | |
| <i>APOE-ε4</i> | 2.12 (1.00-4.52) | .052 | 1.83 (0.74-4.56) | .19 | |
| CG x <i>APOE-ε4</i> | 0.93 (0.78-1.12) | .46 | 0.95 (0.76-1.18) | .64 | |
| Afternoon snack | | | | | |
| GL | 1.13 (0.88-1.53) | .44 | 1.34 (0.84-2.14) | .22 | |
| <i>APOE-ε4</i> | 1.41 (0.94-2.09) | .094 | 1.25 (0.78-2.00) | .35 | |
| GL x <i>APOE-ε4</i> | 1.39 (1.01-1.93) | .045 | 1.52 (1.06-2.24) | .023 | |
| Dinner | | | | | |
| GL | 1.02 (0.91-1.14) | .71 | 0.97 (0.85-1.11) | .65 | |
| <i>APOE-ε4</i> | 1.79 (0.83-3.86) | .14 | 1.72 (0.67-4.39) | .26 | |
| GL x <i>APOE-ε4</i> | 0.97 (0.77-1.21) | .77 | 0.95 (0.72-1.25) | .73 | |

Abbreviations: *APOE-ε4*, Apolipoprotein E ε4 allele; CI, confidence interval; GL, glycemic load; HR, hazard ratio.

NOTE. Proportional hazard models. Model 1 was adjusted for age, sex, education level, energy intake, *APOE-ε4*, BMI, type 2 diabetes, hypertension, cardiovascular history, history of stroke, hypercholesterolemia, history of head trauma, depressive symptomatology, subjective health, and tobacco. Model 2 included additional adjustments for Mediterranean diet-like score and physical activity.

* HR for a 10-point GL increase per day that is equivalent to eating an additional 30 g of French baguette at each corresponding meal.

Supplementary Table 1. Extract from the FFQ used at 1-FU (Bordeaux) and 2-FU (Montpellier), translated from French version. FFQ items from the afternoon snack (between lunch and dinner) are presented.

| Between lunch and dinner, what do you eat? | Never or less than once a month | Number of times per month | Number of times per week |
|---|--|---|---|
| Bread | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Rusk | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Butter | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Margarine | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Jam (or honey) | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Pastry | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Cereal | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Dry biscuits | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Jam biscuits | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Chocolate biscuits | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Cakes | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Yogurt | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Cheese | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Fruits | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Eggs | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Charcuterie | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Sweets, chocolate, | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Stewed fruit | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Between lunch and dinner, what do you drink? | Never or less than once a month | Number of times per month | Number of times per week |
| Coffee | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Coffee with milk | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Tea | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Tea with milk | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Chicory | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Hot chocolate | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Milk | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Soup | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Fruit juice | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Soda | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Light soda | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Water | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Wine | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Beer | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |
| Strong alcohols | <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> | 1 <input type="radio"/> 2 <input type="radio"/> 3 <input type="radio"/> 4 <input type="radio"/> 5 <input type="radio"/> 6 <input type="radio"/> 7 <input type="radio"/> |

Supplementary Table 2. Characteristics of the study population according to daily glyceic load tercile (per day)

| Characteristics | Mean (SD) or n (%) | | |
|-------------------------------------|--------------------|---------------|---------------------|
| | Lower (<90) | Middle (90 to | Upper (\geq 115) |
| Montpellier center | 377 (40.7) | 418 (45.2) | 581 (62.6) |
| Age (years) | 75.98 (4.9) | 75.52 (4.9) | 76.28 (4.9) |
| Women | 600 (64.9) | 542 (58.7) | 554 (59.7) |
| Education level | | | |
| No school | 260 (28.1) | 245 (26.5) | 232 (25.0) |
| Primary school | 267 (28.9) | 270 (29.2) | 247 (26.6) |
| High school | 203 (22.0) | 207 (22.4) | 225 (24.3) |
| Graduated | 194 (21.0) | 199 (21.5) | 221 (23.8) |
| MMSE | 28 (27-29) | 28 (27-29) | 28 (27-29) |
| <i>APOE</i> - ϵ 4 carriers | 156 (16.9) | 172 (18.6) | 154 (16.6) |
| BMI (kg/m ²) | 26.3 (4.2) | 25.81 (4.0) | 24.9 (3.4) |
| Type 2 diabetes | 129 (14.0) | 84 (9.1) | 68 (7.3) |
| Hypertension | 596 (64.4) | 555 (60.1) | 525 (56.6) |
| Cardiovascular history | 115 (12.4) | 103 (11.2) | 89 (9.6) |
| Stroke | 41 (4.4) | 32 (3.5) | 43 (4.6) |
| Hypercholesterolemia | 501 (54.2) | 537 (58.1) | 498 (53.7) |
| Head trauma | 54 (5.84) | 53 (5.7) | 69 (7.4) |
| Depressive | 81 (8.76) | 59 (6.4) | 80 (8.6) |
| Good subjective health | 887 (95.9) | 885 (95.8) | 885 (95.4) |
| Tobacco use (current or | 384 (41.5) | 349 (37.8) | 333 (35.9) |
| Mediterranean diet-like | 4.14 (1.5) | 4.75 (1.6) | 5.2 (1.5) |
| Physical activity | 256 (27.7) | 295 (31.9) | 343 (37.0) |
| Energy intake (kJ/day) | 3533 (686) | 4660 (652) | 6355 (1464) |

*evaluated with the Center for Epidemiological Studies-Depression scale. Abbreviations: *APOE*- ϵ 4, apolipoprotein E ϵ 4 allele; BMI, body mass index; MMSE, Mini Mental State Examination; SD, standard deviation.

Supplementary Table 3. Association between glycemic load terciles of each meal and risk of dementia over 11.4 ± 2 years of follow-up. Daily GL terciles was $GL < 90$, $90 < GL < 115$ and $GL \geq 115$ per day. Breakfast GL terciles was $GL < 20$, $20 < GL < 30$ and $GL \geq 30$ per day. Lunch GL terciles was $GL < 30$, $30 < GL < 37$ and $GL \geq 37$ per day. Afternoon-snack GL terciles was $GL = 0$, $0 < GL < 10$ and $GL \geq 10$ per day. Dinner GL terciles was $GL < 29$, $29 < GL < 38$ and $GL \geq 38$ per day.

| Exposure | Model 1 n = 2,317 | | Model 2 n = 1,934 | |
|-------------------------|----------------------|---------|----------------------|---------|
| | HR*(CI) | P value | HR*(CI) | P value |
| Daily | | | | |
| Lower | (ref) | | (ref) | |
| Middle | 1.02 (0.72-1.44) | .932 | 1.02(0.68-1.54) | .91 |
| Upper | 1.23 (0.79-1.91) | .371 | 1.35(0.8-2.27) | .267 |
| <i>APOE-ε4</i> | 2.15 (1.35-3.42) | .001 | 2.23(1.32-3.76) | .003 |
| Lower x <i>APOE-ε4</i> | (ref) | | (ref) | |
| Middle x <i>APOE-ε4</i> | 0.84 (0.44-1.6) | .593 | 0.82(0.39-1.72) | .591 |
| Upper x <i>APOE-ε4</i> | 1.00 (0.53-1.88) | .991 | 0.95(0.46-1.96) | .884 |
| Breakfast | | | | |
| Lower | (ref) | | (ref) | |
| Middle | 0.94 (0.68-1.31) | .731 | 1.01(0.69-1.47) | .952 |
| Upper | 0.92 (0.6-1.41) | .706 | 0.93(0.57-1.53) | .777 |
| <i>APOE-ε4</i> | 1.56 (0.96-2.51) | .07 | 1.54(0.88-2.7) | .133 |
| Lower x <i>APOE-ε4</i> | (ref) | | (ref) | |
| Middle x <i>APOE-ε4</i> | 1.55 (0.82-2.92) | .179 | 1.75 (0.85-3.63) | .129 |
| Upper x <i>APOE-ε4</i> | 1.35 (0.7-2.61) | .367 | 1.20 (0.55-2.62) | .647 |
| Lunch | | | | |
| Lower | (ref) | | (ref) | |
| Middle | 0.92 (0.65-1.31) | .655 | 0.92 (0.61-1.37) | .669 |
| Upper | 1.13 (0.73-1.74) | .582 | 1.15 (0.7-1.91) | .577 |
| <i>APOE-ε4</i> | 2.16 (1.39-3.35) | .001 | 2.19 (1.33-3.63) | .002 |
| Lower x <i>APOE-ε4</i> | (ref) | | (ref) | |

| | | | | |
|------------------------------------|------------------|--------------------|------------------|--------------------|
| Middle x <i>APOE</i> - | 0.93 (0.5-1.73) | .826 | 0.91 (0.45-1.85) | .79 |
| Upper x <i>APOE</i> - ϵ 4 | 0.90 (0.48-1.7) | .75 | 0.91 (0.43-1.91) | .798 |
| Afternoon snack | | | | |
| Lower | (ref) | | (ref) | |
| Middle | 1.06 (0.76-1.46) | .745 | 1.06 (0.73-1.52) | .773 |
| Upper | 0.99 (0.63-1.58) | .978 | 0.96 (0.57-1.63) | .881 |
| <i>APOE</i> - ϵ 4 | 1.42 (0.89-2.25) | .141 | 1.16 (0.67-2.01) | .598 |
| Lower x <i>APOE</i> - ϵ 4 | (ref) | | (ref) | |
| Middle x <i>APOE</i> - | 1.27 (0.65-2.46) | .481 | 1.73 (0.8-3.74) | .162 |
| Upper x <i>APOE</i> - ϵ 4 | 2.25 (1.21-4.18) | .01 | 3.26(1.57-6.79) | .002 |
| Dinner | | | | |
| Lower | (ref) | | (ref) | |
| Middle | 0.95 (0.67-1.35) | .763 | 1.13 (0.75-1.69) | .568 |
| Upper | 0.82 (0.51-1.32) | .42 | 0.89 (0.51-1.55) | .67 |
| <i>APOE</i> - ϵ 4 | 2.69 (1.75-4.12) | <.000 ₁ | 2.77 (1.65-4.64) | <.000 ₁ |
| Lower x <i>APOE</i> - ϵ 4 | (ref) | | (ref) | |
| Middle x <i>APOE</i> - | 0.64 (0.33-1.21) | .167 | 0.59 (0.28-1.25) | .166 |
| Upper x <i>APOE</i> - ϵ 4 | 0.66 (0.36-1.21) | .18 | 0.68 (0.33-1.4) | .297 |

Abbreviations: *APOE*- ϵ 4, Apolipoprotein E ϵ 4 allele; CI, confidence interval; GL, glycemic load; HR, hazard ratio.

NOTE. Proportional hazard models. Model 1 was adjusted for inclusion center, age, sex, education level, energy intake, *APOE*- ϵ 4, BMI, hypertension, cardiovascular history, history of stroke, hypercholesterolemia, history of head trauma, depressive symptomatology, subjective health, and tobacco. Model 2 included additional adjustments for Mediterranean diet-like score and physical activity.

* HR for a 10-point GL increase per day that is equivalent to eating an additional 30 g of French baguette at each corresponding meal.

Supplementary Table 4. Association between glycemc load and risk of dementia during 11.4 ± 2 years without participants with type 2 diabetes.

| Exposure | Model 1 n = 2,317 | | Model 2 n = 1,934 | |
|-----------------|----------------------|-------------|----------------------|-------------|
| | HR*(CI) | P value | HR*(CI) | P value |
| Daily | | | | |
| GL | 0.99 (0.90-1.09) | .84 | 0.99 (0.89-1.10) | .83 |
| APOE-ε4 | 1.03 (0.37-2.91) | .95 | 0.89 (0.26-3.03) | .85 |
| GL x APOE-ε4 | 1.07 (0.98-1.16) | .15 | 1.08 (0.97-1.19) | .17 |
| Breakfast | | | | |
| GL | 1.01 (0.84-1.22) | .93 | 1.01 (0.81-1.25) | .95 |
| APOE-ε4 | 1.46 (0.74-2.87) | .27 | 1.55 (0.70-3.42) | .28 |
| GL x APOE- | 1.15 (0.92-1.44) | .22 | 1.1 (0.85-1.44) | .46 |
| Lunch | | | | |
| GL | 0.80 (0.62-1.04) | .091 | 0.81 (0.60-1.10) | .17 |
| APOE-ε4 | 2.29 (0.84-6.23) | .11 | 3.21 (0.97-10.6) | .056 |
| CG x APOE-ε4 | 0.98 (0.74-1.30) | .88 | 0.87 (0.61-1.23) | .43 |
| Afternoon snack | | | | |
| GL | 1.15 (0.86-1.54) | .35 | 1.19 (0.84-1.69) | .33 |
| APOE-ε4 | 1.58(1.09-2.29) | .016 | 1.43(0.92-2.21) | .113 |
| GL x APOE- | 1.38 (1.01-1.75) | .008 | 1.47 (1.11-1.93) | .007 |
| Dinner | | | | |
| GL | 0.94 (0.75-1.19) | .62 | 0.96 (0.73-1.26) | .78 |
| APOE-ε4 | 2.74 (1.17-6.40) | .02 | 2.29 (0.78-6.78) | .13 |
| GL x APOE- | 0.93 (0.73-1.17) | .53 | 0.96 (0.71-1.29) | .80 |

$\epsilon 4$

Abbreviations: *APOE- $\epsilon 4$* , Apolipoprotein E $\epsilon 4$ allele; CI, confidence interval; GL, glycemic load; HR, hazard ratio.

NOTE. Proportional hazard models. Model 1 was adjusted for inclusion center, age, sex, education level, energy intake, *APOE- $\epsilon 4$* , BMI, hypertension, cardiovascular history, history of stroke, hypercholesterolemia, history of head trauma, depressive symptomatology, subjective health, and tobacco. Model 2 included additional adjustments for Mediterranean diet-like score and physical activity.

* HR for a 10-point GL increase per day that is equivalent to eating an additional 30 g of French baguette at each corresponding meal.

Supplementary Table 5. Association between glycemic load and risk of Alzheimer's disease (exclusion of participants with mixed dementia and vascular dementia) during 11.4 ± 2 years of follow-up.

| Exposure | Model 1 n = 2,489 | | Model 2 n = 2,078 | |
|--|----------------------|---------|----------------------|---------|
| | HR*(CI) | P value | HR*(CI) | P value |
| Daily | | | | |
| GL | 1.02 (0.92-1.12) | .73 | 1.06 (0.94-1.19) | .33 |
| <i>APOE-$\epsilon 4$</i> | 0.86 (0.29-2.56) | .79 | 0.89 (0.25-3.18) | .86 |
| GL x <i>APOE-$\epsilon 4$</i> | 1.09 (0.99-1.19) | .072 | 1.08 (0.97-1.20) | .16 |
| Breakfast | | | | |
| GL | 0.99 (0.80-1.21) | .89 | 1.03 (0.81-1.30) | .82 |
| <i>APOE-$\epsilon 4$</i> | 1.26 (0.62-2.56) | .52 | 1.59 (0.70-3.62) | .27 |
| GL x <i>APOE-$\epsilon 4$</i> | 1.24 (0.98-1.56) | .075 | 1.12 (0.85-1.47) | .43 |
| Lunch | | | | |
| GL | 0.96 (0.73-1.27) | .78 | 1.07 (0.77-1.49) | .69 |
| <i>APOE-$\epsilon 4$</i> | 2.02 (0.69-5.87) | .20 | 2.68 (0.74-9.63) | .13 |
| CG x <i>APOE-$\epsilon 4$</i> | 1.03 (0.76-1.39) | .85 | 0.94 (0.65-1.35) | .72 |
| Afternoon snack | | | | |

| | | | | | |
|--------|--------------------------|------------------|------------|------------------|------------|
| | GL | 1.30 (0.95-1.76) | .10 | 1.41 (0.97-2.04) | .07 |
| | <i>APOE</i> -ε4 | 1.72 (1.16-2.54) | .007 | 1.60 (1.01-2.52) | .043 |
| | GL x <i>APOE</i> - | 1.32 (1.04-1.68) | .03 | 1.39 (1.05-1.84) | .02 |
| Dinner | | | | | |
| | GL | 0.91 (0.71-1.17) | .45 | 0.99 (0.73-1.34) | .95 |
| | <i>APOE</i> -ε4 | 2.88 (1.17-7.10) | .02 | 2.97 (0.98-9.00) | .054 |
| | GL x <i>APOE</i> - ε4 | 0.93 (0.72-1.19) | .56 | 0.91 (0.67-1.24) | .54 |

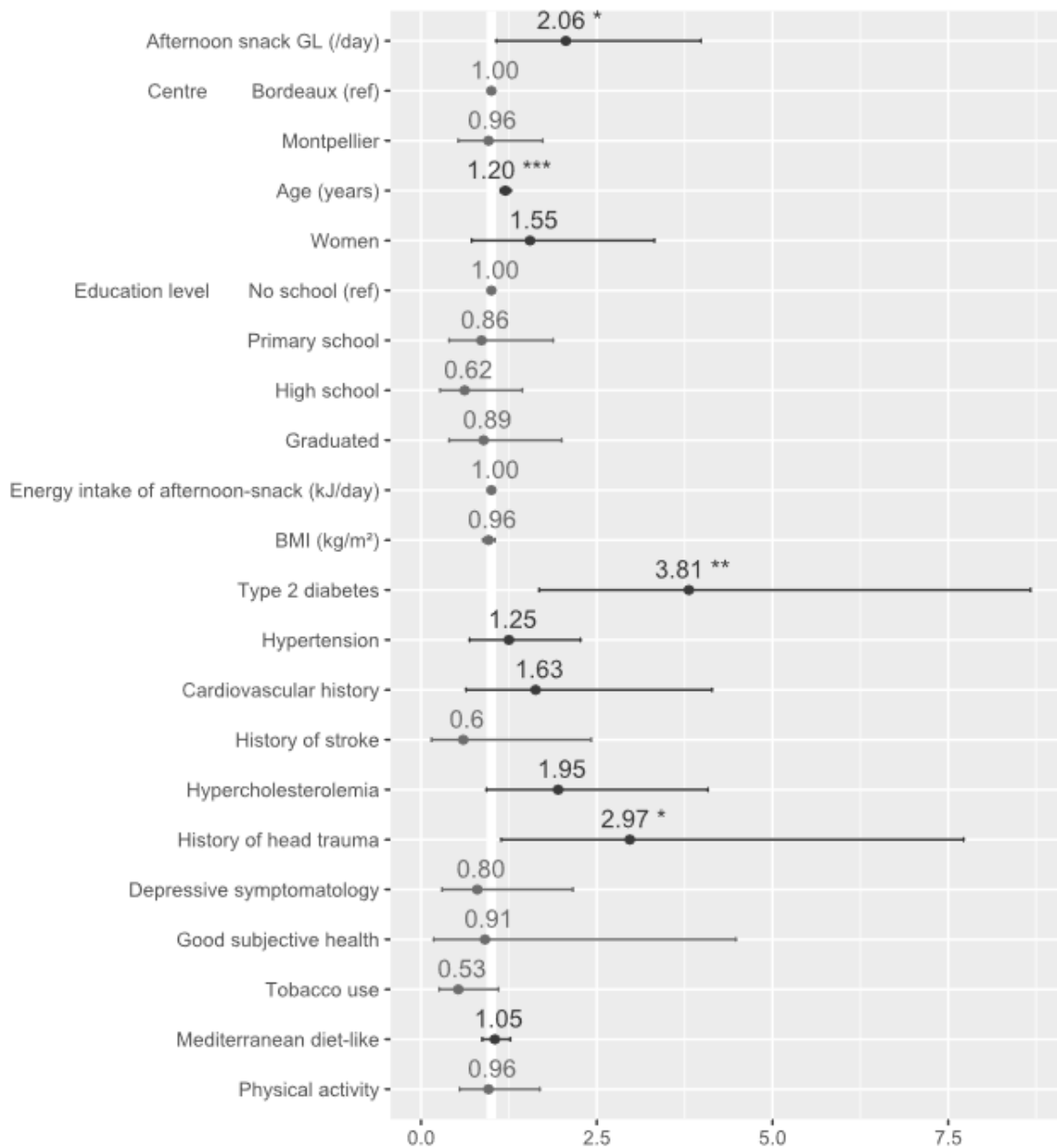
Abbreviations: *APOE*-ε4, Apolipoprotein E ε4 allele; CI, confidence interval; GL, glycemic load; HR, hazard ratio.

NOTE. Proportional hazard models. Model 1 was adjusted for inclusion center, age, sex, education level, energy intake, *APOE*-ε4, BMI, type 2 diabetes, hypertension, cardiovascular history, history of stroke, hypercholesterolemia, history of head trauma, depressive symptomatology, subjective health, and tobacco. Model 2 included additional adjustments for Mediterranean diet-like score and physical activity.

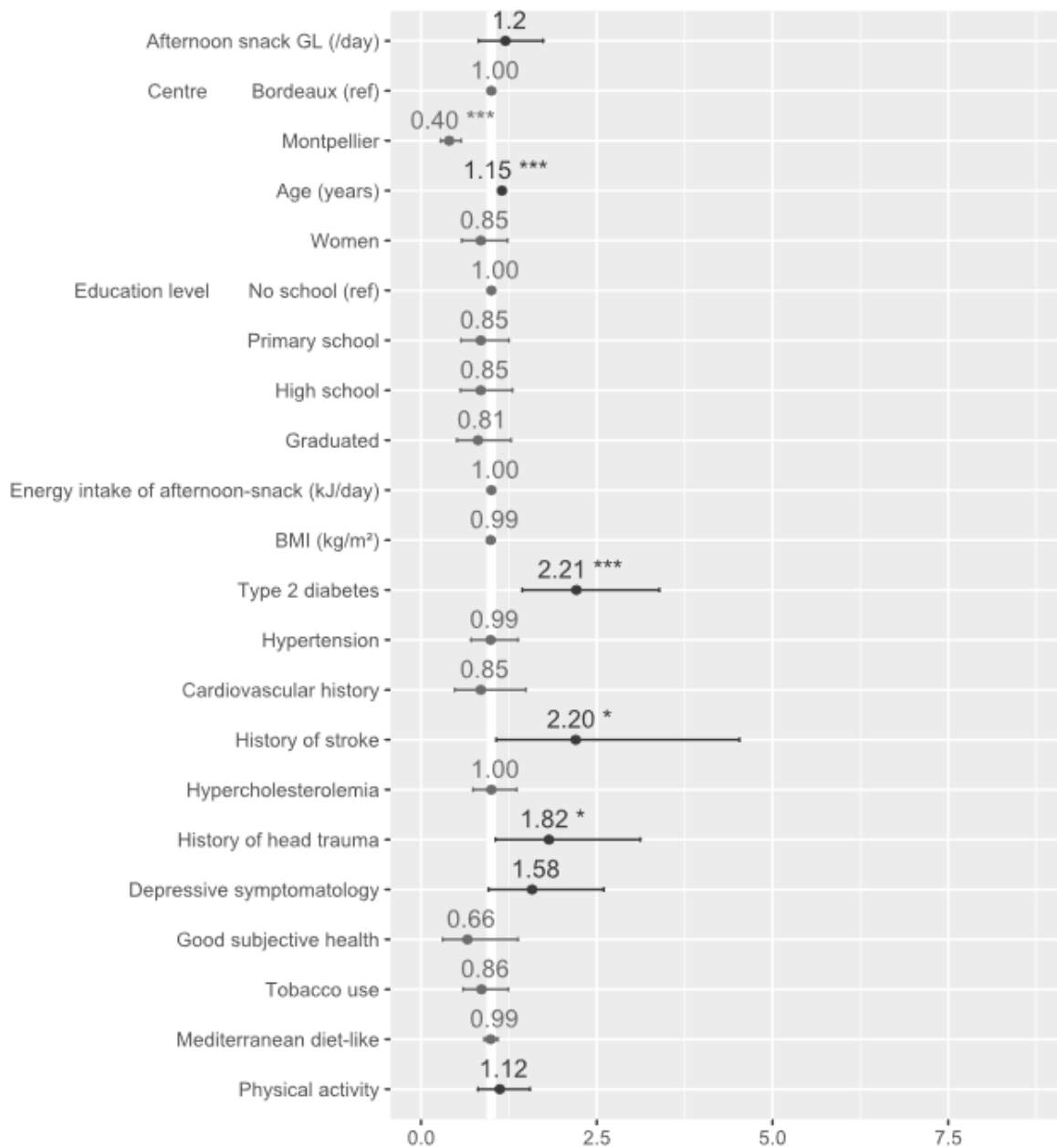
* HR for a 10-point GL increase per day that is equivalent to eating an additional 30 g of French baguette at each corresponding meal.

Supplementary Table 6. Number of servings per week for each meal.

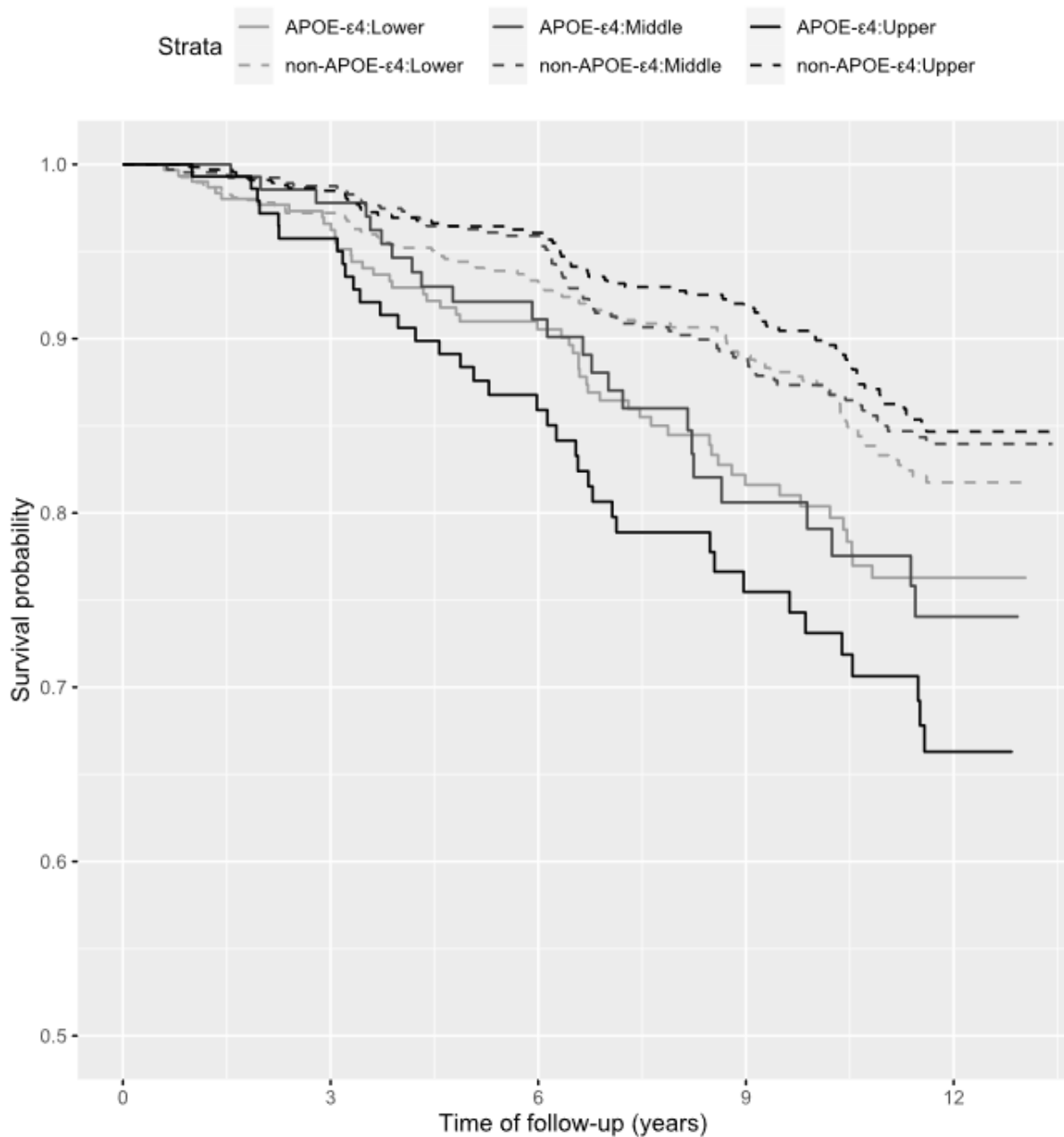
| Food groups | Breakfast | Lunch | Afternoon snack | Dinner |
|--------------------|----------------------------------|------------|-----------------|------------|
| | <i>Mean (standard deviation)</i> | | | |
| Cereals, bread | 6.2 (3.04) | 6.1 (3.04) | 0.4 (1.45) | 5.6 (2.62) |
| Starchy foods | | 4.2 (2.32) | | 2.6 (2.55) |
| Meat, poultry | | 4.5 (3.84) | | 1.7 (1.88) |
| Fish and seafood | | 2.2 (3.05) | | 0.9 (1.23) |
| Eggs, charcuterie | 0.2 (1.12) | 1.6 (3.28) | 0.04 (0.39) | 1.9 (1.79) |
| Vegetables, | | 7.6 (1.12) | | 3.5 (3.21) |
| Fruits | 1.0 (2.32) | 5.1 (3.24) | 0.7 (1.76) | 4.0 (2.95) |
| Biscuits, cakes | 4.2 (3.84) | 1.0 (3.04) | 1.5 (2.69) | 1.3 (1.94) |
| Sweets, chocolate, | 1.8 (3.05) | 0.3 (2.32) | 1.2 (2.43) | 0.2 (0.86) |
| Dairy products | 1.8 (3.28) | 6.3 (3.84) | 0.5 (1.55) | 7.3 (3.76) |
| Coffee, tea | 5.3 (3.24) | 4.1 (3.05) | 1.6 (2.71) | 0.4 (1.60) |



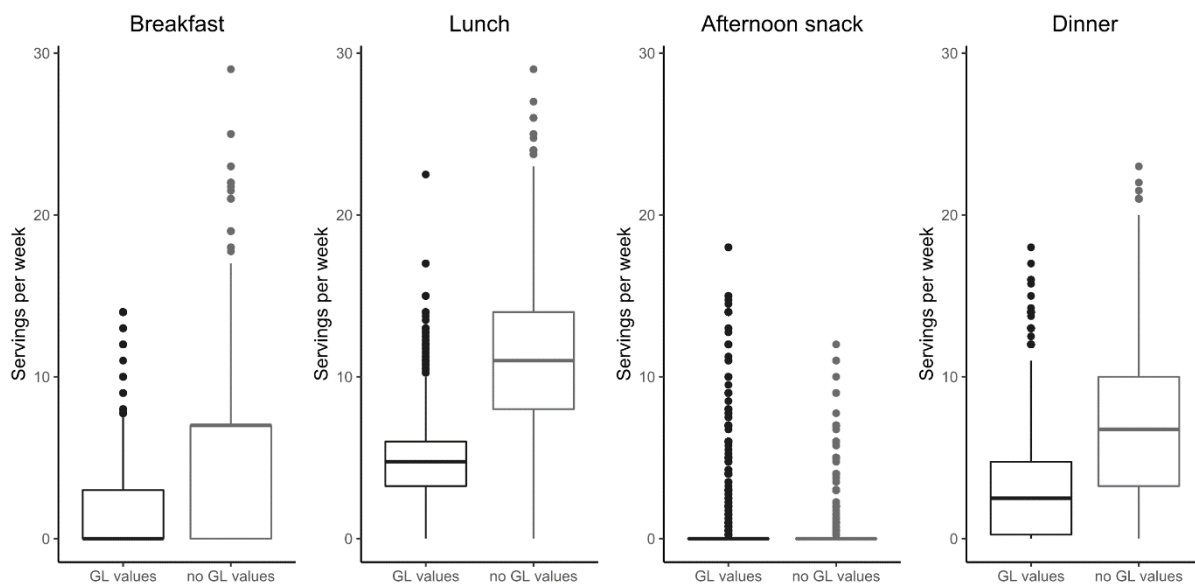
Supplementary Figure 1. Stratified analysis on participants with *APOE*- ϵ 4 status. Estimated hazard ratios of all covariates from Model 2 ($n = 391$). The hazard ratio of the afternoon-snack GL is expressed as a 10-point increase of the GL value per day that is equivalent to eating an additional 30 g of French baguette at each corresponding meal. Abbreviations: *APOE*- ϵ 4, apolipoprotein E ϵ 4 allele; BMI, body mass index; GL, glycemic load. * P value $< .05$; ** P value $< .01$; *** P value $< .001$.



Supplementary Figure 2. Stratified analysis on participants without *APOE-ε4* status. Estimated hazard ratios of all covariates from Model 2 (n = 1,754). The hazard ratio of the afternoon-snack GL is expressed as a 10-point increase of the GL value per day that is equivalent to eating an additional 30 g of French baguette at each corresponding meal. Abbreviations: *APOE-ε4*, apolipoprotein E ε4 allele; BMI, body mass index; GL, glycemic load. * *P* value < .05; ** *P* value < .01; *** *P* value < .001.



Supplementary Figure 3. Kaplan-Meier survival curves according to afternoon-snack GL tertiles and *APOE*- ϵ 4 carriers status. Time to diagnosis of dementia for *APOE*- ϵ 4 carriers participants (solid line) or non-*APOE*- ϵ 4 carriers participants (dashed line) with GL=0 (light grey), $0 < \text{GL} < 10$ (dark grey) or $\text{GL} \geq 10$ per day (black). Abbreviations: *APOE*- ϵ 4, apolipoprotein E ϵ 4 allele; GL, glycemic load.



Supplementary Figure. 4. Servings per week of the FFQ items according to their glycemic load values: no GL value (e.g., meat, fish, fat) and GL values.

Abbreviations: FFQ, Food Frequency Questionnaire; GL, glycemic load.