

FEATURED ARTICLE

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

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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 the 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 (GL) was quantified in 2777 elderly participants from the French Three-City Study to estimate RF intake. Then, the associations between GL 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 GL was associated with increased dementia and AD risk in *APOE- ϵ 4* carriers (hazard ratio = 1.27 [1.03–1.56]).

Discussion: This study highlights that RF-rich diets are a risk factor for dementia and AD in *APOE- ϵ 4* carriers.

KEYWORDS

Alzheimer's disease, apolipoprotein E ϵ 4, cohort study, dementia, diet, glycemic load, refined carbohydrate, sugar

1 | INTRODUCTION

According to the World Health Organization, dementia will affect >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 (ie, 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 ($A\beta$) deposits. These studies also demonstrated that a high-sugar diet alters brain insulin signaling 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, a 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 (GL).^{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 a 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 GL, 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 a 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- ϵ 4? (4) Is the association independent of T2D?

2 | METHODS

2.1 | Study participants

The Three-City Study is a French population-based cohort study of 9294 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; Figure 1). Questionnaires were used to collect data on sociodemographic 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 (ie, 2 and 4 years after baseline), respectively (Figure 1). Participants with prevalent dementia at the time of FFQ completion were excluded. A flow chart describes the participants' selection (Figure 2). At the end of the study, the mortality rate was

HIGHLIGHTS

- Afternoon snacks rich in refined carbohydrates are associated with increased dementia and Alzheimer's disease risk in apolipoprotein E ϵ 4 allele (APOE- ϵ 4) carriers.
- The risks of dementia within 12 years are 1.27-fold higher in APOE- ϵ 4 carriers with higher glycemic load (equivalent to an additional 30 g of French baguette) at the afternoon snack.
- The refined carbohydrate intake at breakfast, lunch, and dinner is not associated with the risk of dementia.

RESEARCH IN CONTEXT

1. Systematic review: We searched for relevant literature using the online PubMed database. We noted the scarcity of published studies on the association between "dementia" [Mesh] or "cognitive dysfunction" [Mesh] and "sugar(s)," "carbohydrate(s)," "glyc(a)emic index" or "glyc(a)emic load." We observed that most of the retrieved studies had a cross-sectional design and/or a small sample size.
2. Interpretation: Our findings show an association between afternoon snacks with high refined carbohydrates and dementia risk in carriers of the apolipoprotein ϵ 4 allele.
3. Future directions: Prospective studies are required to confirm our results. Experimental studies are needed to explore the relationships among refined carbohydrate consumption, glycemic response, and apolipoprotein E4 in dementia pathophysiology.

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 (Figure 1). The FFQ was divided into: breakfast, lunch, dinner, and snacks between meals (extract from the FFQ in Table S1 in supporting information). 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.

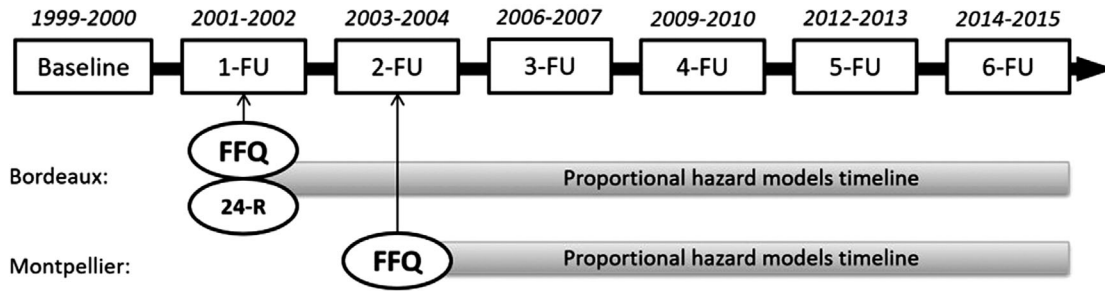


FIGURE 1 Time frame of the Three-City Study at the Bordeaux and Montpellier centers. Diagnosis of dementia is made at each follow-up visit (FU). The food frequency questionnaire (FFQ) was completed by participants at 1-FU in Bordeaux and at 2-FU in Montpellier. The 24-hour dietary recall (24-R) was only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

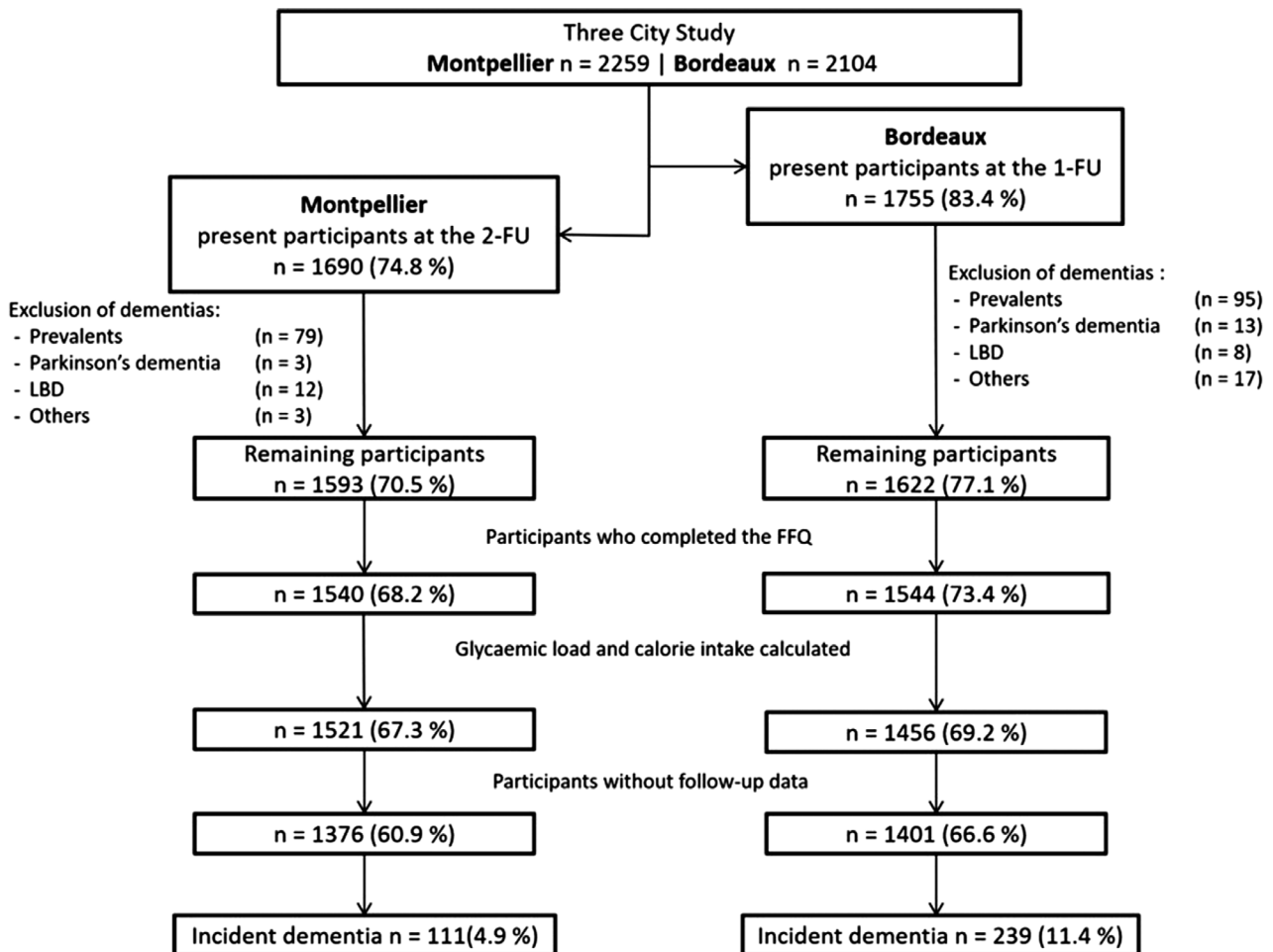


FIGURE 2 Flow chart of the study sample from the Bordeaux and Montpellier centers of the Three-City Study. Abbreviations: FFQ, Food frequency questionnaire; FU, follow-up; LBD, Lewy Body Dementia

2.2.2 | Twenty-four-hour dietary recall interview

A 24-hour 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-hour dietary recall was previously checked for fatty acids.¹⁹ These data were only used in sensitivity analyses.

2.2.3 | Glycemic load

The glycemic index values of FFQ items were obtained from the International Table of Glycemic Index²⁰ and internet updates (www.glycemicindex.com), using glucose as the reference. The glycemic index compares the rate of glucose release by measuring the 2 hours postprandial glycemia after consumption of a food portion

containing 50 g of available carbohydrates. GL reflects both the carbohydrate quantity and quality.^{20,21} Compared to low-GL diets, high-GL diets elicit larger glycemic and insulinemic responses.^{9,12,20} For each FFQ item (ie, 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 (eg, 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-hour 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-hour dietary recall. The total GL values for breakfast, lunch, afternoon snack, and dinner from the FFQ and the 24-hour 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-Ciquel database (www.anses.ciquel.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-hour 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-hour dietary recall in the Bordeaux subsample were significantly correlated (range: 0.20 to 0.53).

2.2.5 | Mediterranean-like diet score

To take into account the diet quality, a Mediterranean-like diet score was calculated. Items were grouped according to the nine components of the Mediterranean-like diet score.^{24,25} For fruits, vegetables, legumes, cereals, and fish, one point was assigned when the participant's consumption was above the median, zero otherwise. For meat and dairy, one point was assigned when the participant's consumption was below the median, zero otherwise. For alcohol, one point was assigned when consumption was below 20 g of ethanol per day for men and 5.7 g for women (ie, low-to-moderate alcohol consumption in this population). For the ratio of monounsaturated fatty acids to saturated fatty acids, one point was assigned when the ratio was above the sex-specific median, zero otherwise. The total Mediterranean-like diet score ranged from zero (lowest adherence) to nine (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 etiology 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 graduate level. The Mini-Mental State Examination³⁰ 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 glycaemia >7 mmol.L⁻¹, and additionally self-reported. APOE 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 analysis of variance (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- to 13-year follow-up (mean follow-up = 11.4 ± 2 years), in five separated analyses (ie, daily, breakfast, lunch, afternoon snack, dinner). This modeling considers the time of dementia onset and the participants out of the study (ie, death, loss of follow-up). In Model 1, analyses were adjusted for 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 (ie, 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 Schönfeld 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 the 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-hour 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 2777 participants ($n = 1376$ from Montpellier and $n = 1401$ from Bordeaux) were included in the analyses (Table 1, Table S2 in supporting information). 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 glycemic 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-ε4* carrier status was significantly associated with the dementia risk. *APOE-ε4* carrier status was also associated with the dementia risk. After adjustments for Mediterranean-like diet score and physical activity (Model 2), the interaction remained significant. Significant covariates were *APOE-ε4* carrier status, age, T2D, and history of head trauma as risk factors and living in Montpellier as protective factor (Figure 3). Multiple imputations (Model 3) did not change these results showing that the risk of dementia was higher in *APOE-ε4* carriers who consumed afternoon snacks with high GL value. To quantify this association, we stratified by *APOE-ε4* (Figure S1, S2 in supporting information). In *APOE-ε4* 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-ε4* carrier status was significantly associated with the dementia risk (Table S3 in supporting information). Kaplan-Meier survival curves clearly illustrated it (Figure S3 in supporting information).

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-hour dietary recall (Table 3). Proportional hazards models confirmed that the interaction between afternoon-snack GL and *APOE-ε4* carrier status was associated with dementia. Hazard ratios

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	
APOE-ε4 carriers	482 (17.5)		5.3
BMI (kg/m ²)	25.7 (3.9)	13.59–45.18	
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 symptomatology ^a	220 (7.92)		
Good subjective health	2657 (95.7)		
Tobacco use (current or past)	1066 (38.4)		
Mediterranean-like diet	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)	1311–15925	

Abbreviations: APOE-ε4, apolipoprotein E ε4 allele; BMI, body mass index; IQR, interquartile range; MMSE, Mini Mental State Examination; SD, standard deviation.

^aEvaluated with the Center for Epidemiological Studies-Depression scale.

estimated from the 24-hour 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 (Table S4 in supporting information). 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 (Table S5 in supporting information).

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 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. did not find any significant effect of

TABLE 2 Association between glycaemic load and risk of dementia over 11.4 ± 2 years of follow-up

Exposure	Model 1 n = 2572		Model 2 n = 2145		Model 3 n = 2777	
	HR ^a (CI)	P value	HR ^a (CI)	P value	HR ^a (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
APOE-ε4	1.12 (0.44–2.90)	.81	1.14 (0.38–3.40)	.82	1.32 (0.53–3.29)	.56
GL x APOE-ε4	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
APOE-ε4	1.46 (0.79–2.70)	.23	1.80 (0.89–3.64)	.10	1.58 (0.88–2.85)	.12
GL x APOE-ε4	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
APOE-ε4	2.07 (0.82–5.2)	.12	2.65 (0.90–7.84)	.078	2.16 (0.88–5.29)	.093
CG x APOE-ε4	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
APOE-ε4	1.59 (1.14–2.22)	.007	1.53 (1.04–2.25)	.03	1.65 (1.20–2.28)	.002
GL x APOE-ε4	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
APOE-ε4	2.73 (1.25–5.96)	.012	2.65 (1.03–6.86)	.044	2.84 (1.33–6.08)	.007
GL x APOE-ε4	0.91 (0.73–1.14)	.42	0.92 (0.71–1.20)	.56	0.91 (0.73–1.12)	.36

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

NOTE. Proportional hazard models. Model 1 was adjusted for inclusion centre, age, sex, education level, energy intake, APOE-ε4 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-like diet score and physical activity. Model 3 is Model 2 with multiple imputations^aHR 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.

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 favorable 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 sodas⁴ (Table S6, Figure S4 in supporting information). Snacks are digested more rapidly than full meals because of their lower content in fat and fiber. 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 signaling in the cortex, and the hippocampus in an age-dependent manner.¹⁶ Moreover, in these mice, the transcription factor

peroxisome proliferator-activated receptor gamma, which increases insulin sensitivity, is downregulated,^{47,48} and glucose metabolism in the 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

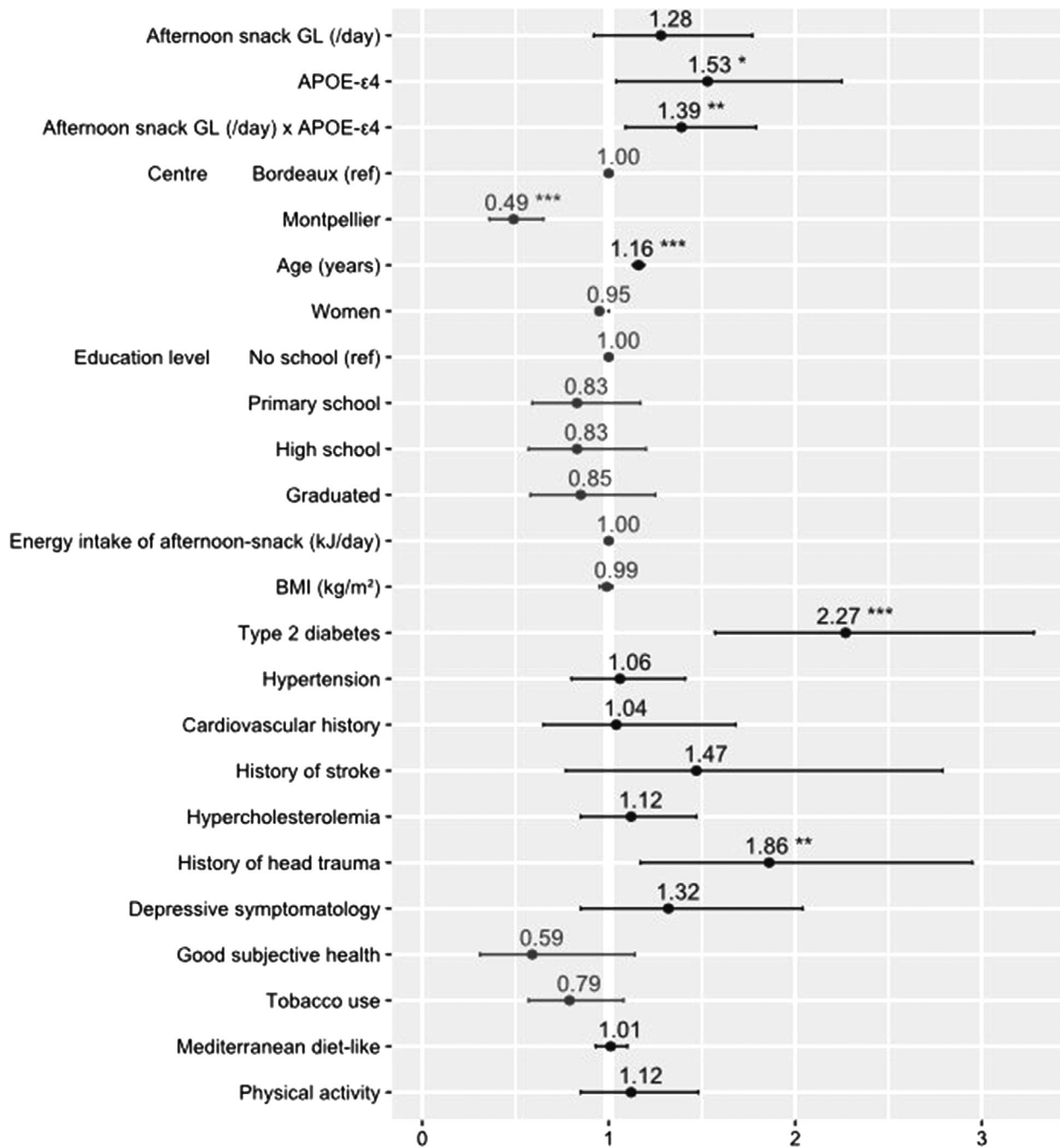


FIGURE 3 Estimated hazard ratios of all covariates from Model 2 (n = 2145). The hazard ratio of the afternoon-snack GL is expressed as a 10-point increase of the GL value per day that is equivalent to eating an additional 30 g of French baguette at each corresponding meal. Abbreviations: APOE-ε4, apolipoprotein E ε4 allele; BMI, body mass index; GL, glycemic load. * P value < .05; ** P value < .01; *** P value < .001.

of all food together (ie, 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 fibers 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 (eg, rice) are eaten first and then vegetables and meat compared to 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-hour dietary recall (Bordeaux subsample) validated the results obtained with the FFQ. Moreover, we adjusted for numerous confounding factors. Specifically, our results are

TABLE 3 Association between the glycaemic load, estimated from the 24-h dietary recall interview (Bordeaux centre), and the risk of dementia during 13 years of follow-up

Exposure	Model 1 n = 1,229		Model 2 n = 954	
	HR ^a (CI)	P value	HR ^a (CI)	P value
Daily				
GL	1.01 (0.96–1.07)	.62	1.01 (0.94–1.07)	.82
APOE-ε4	1.59 (0.58–4.31)	.36	1.45 (0.45–4.65)	.53
GL x APOE-ε4	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
APOE-ε4	1.61 (0.87–2.97)	.13	1.71 (0.82–3.54)	.15
GL x APOE-ε4	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
APOE-ε4	2.12 (1.00–4.52)	.052	1.83 (0.74–4.56)	.19
CG x APOE-ε4	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
APOE-ε4	1.41 (0.94–2.09)	.094	1.25 (0.78–2.00)	.35
GL x APOE-ε4	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
APOE-ε4	1.79 (0.83–3.86)	.14	1.72 (0.67–4.39)	.26
GL x APOE-ε4	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, glycaemic load; HR, hazard ratio.

NOTES: 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-like diet score and physical activity.

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

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-ε4 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-ε4 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-ε4 carriers. These results pave the way to new prevention strategies. However, large-scale studies in different populations and using a homogeneous methodology are required to replicate this observation. Moreover, the statistical interaction between APOE-ε4 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-ε4 in dementia pathophysiology.

ACKNOWLEDGMENTS

The Three City (3C) Study is carried out under a partnership agreement between Inserm, the Victor Segalen–Bordeaux II University, and Sanofi-Synthelabo. The Fondation pour la Recherche Médicale funded the preparation and first phase of the study. The 3C Study is also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, MGEN, the Institut de la Longévité, Agence Française de Sécurité Sanitaire des Produits de Santé, the Regional Governments of Aquitaine, Bourgogne and Languedoc-Roussillon, Fondation de France, and the Ministry of Research-Inserm Programme “Cohorts and collection of biological material.”

This study was also supported by Union France Alzheimer.

None of the funding organizations or sponsors played a role in the study design and conduct; in the data collection, management, analysis, or interpretation; or in the preparation, review, or approval of the manuscript.

This is contribution ISEM 2020 – 090 of the Institute of Evolutionary Science of Montpellier.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

REFERENCES

- World Health Organization. *Dementia*. WHO; 2019. <https://www.who.int/news-room/fact-sheets/detail/dementia>. Accessed June 11, 2019.
- Scarmeas N, Anastasiou CA, Yannakoulia M. Nutrition and prevention of cognitive impairment. *Lancet Neurol*. 2018;17:1006–1015.
- Gross LS, Li L, Ford ES, Liu S. Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecologic assessment. *Am J Clin Nutr*. 2004;79:774–779.
- Bellisle F, Dalix AM, Mennen L, et al. Contribution of snacks and meals in the diet of French adults: a diet-diary study. *Physiol Behav*. 2003;79:183–189.
- Cao D, Lu H, Lewis TL, Li L. Intake of sucrose-sweetened water induces insulin resistance and exacerbates memory deficits and amyloidosis in a transgenic mouse model of Alzheimer disease. *J Biol Chem*. 2007;282:36275–36282.
- Orr ME, Salinas A, Buffenstein R, Oddo S. Mammalian target of rapamycin hyperactivity mediates the detrimental effects of a high sucrose diet on Alzheimer's disease pathology. *Neurobiol Aging*. 2014;35:1233–1242.
- Arnold SE, Arvanitakis Z, Macauley-Rambach SL, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. *Nat Rev Neurol*. 2018;14:168–181.

8. Philippou E, Constantinou M. The influence of glycemic index on cognitive functioning: a systematic review of the evidence. *Adv Nutr Bethesda Md*. 2014;5:119-130.
9. Gilsenan MB, de Bruin EA, Dye L. The influence of carbohydrate on cognitive performance: a critical evaluation from the perspective of glycaemic load. *Br J Nutr*. 2009;101:941-949.
10. Taylor MK, Sullivan DK, Swerdlow RH, et al. A high-glycemic diet is associated with cerebral amyloid burden in cognitively normal older adults. *Am J Clin Nutr*. 2017;106:1463-1470.
11. Staubo SC, Aakre JA, Vemuri P, et al. Mediterranean diet, micronutrients and macronutrients, and MRI measures of cortical thickness. *Alzheimers Dement*. 2017;13:168-177.
12. Power SE, O'Connor EM, Ross RP, et al. Dietary glycaemic load associated with cognitive performance in elderly subjects. *Eur J Nutr*. 2015;54:557-568.
13. Sindi S, Kåreholt I, Eskelinen M, et al. Healthy dietary changes in midlife are associated with reduced dementia risk later in life. *Nutrients*. 2018;10:1649.
14. Seetharaman S, Andel R, McEvoy C, Dahl Aslan AK, Finkel D, Pedersen NL. Blood glucose, diet-based glycemic load and cognitive aging among dementia-free older adults. *J Gerontol Ser A*. 2015;70:471-479.
15. Luchsinger JA, Tang MX, Mayeux R. Glycemic load and risk of Alzheimer's disease. *J Nutr Health Aging*. 2007;11:238-241.
16. Zhao N, Liu C-C, Van Ingelgom AJ, et al. Apolipoprotein E4 impairs neuronal insulin signaling by trapping insulin receptor in the endosomes. *Neuron*. 2017;96:115-129.e5.
17. 3C Study Group. Vascular factors and risk of dementia: design of the Three-City Study and baseline characteristics of the study population. *Neuroepidemiology*. 2003;22:316-325.
18. Samieri C, Jutand M-A, Féart C, Capuron L, Letenneur L, Barberger-Gateau P. Dietary patterns derived by hybrid clustering method in older people: association with cognition, mood, and self-rated health. *J Am Diet Assoc*. 2008;108:1461-1471.
19. Féart C, Jutand MA, Larrieu S, et al. Energy, macronutrient and fatty acid intake of French elderly community dwellers and association with socio-demographic characteristics: data from the Bordeaux sample of the Three-City Study. *Br J Nutr*. 2007;98:1046-1057.
20. Foster-Powell K, Holt SHA, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. *Am J Clin Nutr*. 2002;76:5-56.
21. Salmerón J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. *JAMA*. 1997;277:472-477.
22. Monro JA, Shaw M. Glycemic impact, glycemic glucose equivalents, glycemic index, and glycemic load: definitions, distinctions, and implications. *Am J Clin Nutr*. 2008;87:2375-2435.
23. van Bakel MME, Kaaks R, Feskens EJM, et al. Dietary glycaemic index and glycaemic load in the European Prospective Investigation into Cancer and Nutrition. *Eur J Clin Nutr*. 2009;63:S188-S205.
24. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. *N Engl J Med*. 2003;348:2599-2608.
25. Féart C, Samieri C, Rondeau V, et al. Adherence to a Mediterranean diet, cognitive decline, and risk of dementia. *JAMA*. 2009;302:638-648.
26. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000.
27. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology*. 1984;34:939-944.
28. Román GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology*. 1993;43:250-260.
29. Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills*. 1958;8:271-276.
30. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.
31. Brindel P, Hanon O, Dartigues J-F, et al. Prevalence, awareness, treatment, and control of hypertension in the elderly: the Three City study. *J Hypertens*. 2006;24:51-58.
32. Dufouil C, Richard F, Fiévet N, et al. APOE genotype, cholesterol level, lipid-lowering treatment, and dementia: the Three-City Study. *Neurology*. 2005;64:1531-1538.
33. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1:385-401.
34. Fuhrer R, Rouillon F. La version française de l'échelle CES-D (Center for Epidemiologic Studies-Depression Scale). Description et traduction de l'échelle d'autoévaluation. *Eur Psychiatry*. 1989;4:163-166.
35. Letois F, Mura T, Scali J, Gutierrez L-A, Féart C, Berr C. Nutrition and mortality in the elderly over 10 years of follow-up: the Three-City study. *Br J Nutr*. 2016;116:882-889.
36. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol*. 2014;13:788-794.
37. van Buuren S. *Flexible Imputation of Missing Data*. 2nd ed. Boca Raton, FL: Chapman & Hall/CRC; 2018.
38. Shah AD, Bartlett JW, Carpenter J, Nicholas O, Hemingway H. Comparison of random forest and parametric imputation models for imputing missing data using MICE: a CALIBER study. *Am J Epidemiol*. 2014;179:764-774.
39. Pase MP, Himali JJ, Jacques PF, et al. Sugary beverage intake and preclinical Alzheimer's disease in the community. *Alzheimers Dement*. 2017;13:955-964.
40. Pase MP, Himali JJ, Beiser AS, et al. Sugar- and artificially sweetened beverages and the risks of incident stroke and dementia: a prospective cohort study. *Stroke*. 2017;48:1139-1146.
41. Peila R, Rodriguez BL, Launer LJ. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study. *Diabetes*. 2002;51:1256-1262.
42. Bangen KJ, Himali JJ, Beiser AS, et al. Interaction between midlife blood glucose and APOE genotype predicts later Alzheimer pathology. *J Alzheimers Dis JAD*. 2016;53:1553-1562.
43. Schrijvers EMC, Wittman JCM, Sijbrands EJJ, Hofman A, Koudstaal PJ, Breteler MMB. Insulin metabolism and the risk of Alzheimer disease. *Neurology*. 2010;75:1982-1987.
44. Butterfield DA, Di Domenico F, Barone E. Elevated risk of type 2 diabetes for development of Alzheimer disease: a key role for oxidative stress in brain. *Biochim Biophys Acta*. 2014;1842:1693-1706.
45. Nolan CJ, Ruderman NB, Kahn SE, Pedersen O, Prentki M. Insulin resistance as a physiological defense against metabolic stress: implications for the management of subsets of type 2 diabetes. *Diabetes*. 2015;64:673-686.
46. Jofre-Monseny L, Minihane A-M, Rimbach G. Impact of apoE genotype on oxidative stress, inflammation and disease risk. *Mol Nutr Food Res*. 2008;52:131-145.
47. Keeney JT-R, Ibrahim S, Zhao L. Human ApoE isoforms differentially modulate glucose and amyloid metabolic pathways in female brain: evidence of the mechanism of neuroprotection by ApoE2 and implications for Alzheimer's disease prevention and early intervention. *J Alzheimers Dis JAD*. 2015;48:411-424.
48. Wu L, Zhang X, Zhao L. Human ApoE isoforms differentially modulate brain glucose and ketone body metabolism: implications for Alzheimer's disease risk reduction and early intervention. *J Neurosci Off J Soc Neurosci*. 2018;38:6665-6681.

49. Reiman EM, Chen K, Alexander GE, et al. Correlations between apolipoprotein E epsilon4 gene dose and brain-imaging measurements of regional hypometabolism. *Proc Natl Acad Sci U S A*. 2005;102:8299-8302.
50. Rimajova M, Lenzo NP, Wu J-S, et al. Fluoro-2-deoxy-D-glucose (FDG)-PET in APOEepsilon4 carriers in the Australian population. *J Alzheimers Dis JAD*. 2008;13:137-146.
51. Rönnemaa E, Zethelius B, Sundelöf J, et al. Impaired insulin secretion increases the risk of Alzheimer disease. *Neurology*. 2008;71:1065-1071.
52. Hätönen KA, Virtamo J, Eriksson JG, Sinkko HK, Sundvall JE, Valsta LM. Protein and fat modify the glycaemic and insulinaemic responses to a mashed potato-based meal. *Br J Nutr*. 2011;106:248-253.
53. Post RE, Mainous AG, King DE, Simpson KN. Dietary fiber for the treatment of type 2 diabetes mellitus: a meta-analysis. *J Am Board Fam Med JABFM*. 2012;25:16-23.
54. Sun L, Goh HJ, Govindharajulu P, Leow MK-S, Henry CJ. Postprandial glucose, insulin and incretin responses differ by test meal macronutrient ingestion sequence (PATTERN study). *Clin Nutr*. 2020;39:950-957.

SUPPORTING INFORMATION

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

How to cite this article: Gentreau M, Chuy V, Féart C, et al. Refined carbohydrate-rich diet is associated with long-term risk of dementia and Alzheimer's disease in apolipoprotein E ε4 allele carriers. *Alzheimer's Dement*. 2020;1-11.
<https://doi.org/10.1002/alz.12114>