

# **Glucometabolic changes are associated with structural gray matter alterations in prodromal dementia**

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## ABSTRACT

**Background:** Glucometabolic changes, such as high glycemic load (GL) diet and insulin resistance (IR), are potential risk factor of Alzheimer's disease (AD). Yet, the effect of these factors on brain alterations that contribute to AD pathology has not been clearly demonstrated.

**Objective:** We aimed to assess the relationship of GL and IR with gray matter volumes involved in prodromal dementia.

**Methods:** GL and Triglyceride-Glucose (TyG) index, an IR surrogate marker, were calculated in 497 participants who underwent magnetic resonance imaging (MRI). The gray matter volumes most related to prodromal dementia/mild cognitive impairment (diagnosed in 18/158 participants during the 7-year follow-up) were identified using a data-driven machine learning algorithm.

**Results:** Higher GL diet was associated with reduced amygdala volume. The TyG index was negatively associated with the hippocampus, amygdala and putamen volumes.

**Conclusion:** These results suggest that GL and IR are associated with lower gray matter volumes in brain regions involved in AD pathology.

**Keywords:** glycemic load; insulin resistance; magnetic resonance imaging; hippocampus; amygdala; putamen; dementia

## INTRODUCTION

A large body of epidemiological evidence demonstrated the importance of insulin and glucose homeostasis in the development of mild cognitive impairment (MCI) and Alzheimer's disease (AD), to the extent that AD is sometimes referred to as "type 3 diabetes" [1,2]. Cognitive impairment has been associated with insulin resistance (IR) and high glycemia in several epidemiological studies [3,4]. Indeed, IR and high glycemia, typical features of type 2 diabetes, are promoted by high glycemic load (GL) diets [5] that have been recently identified as a potential risk factor of AD and cognitive impairment [4,6]. One of the underlying hypotheses is that high GL diet could promote AD development through IR. However, there is no clear evidence of the impact of glucometabolic changes (e.g. IR, high fasting glycemia, or high GL diet) on brain alterations that might contribute to the AD pathology. For instance, lower total brain volume has been associated with IR [7] and higher serum insulin concentration [8], but not with higher fasting glycemia [9]. Conversely, another study found a significant association between higher fasting glycemia and lower gray matter (GM) volume [10].

Nevertheless, the effect of glucometabolic changes on specific brain volumes remains poorly described. Most studies have focused on hippocampus because within the medial temporal lobe, its reduction has been consistently reported in patients with AD and predicts conversion of MCI to AD [11]. Reduced hippocampal volume has been correlated with high fasting glycemia [9,12] and might have a role in mediating the effects of glycemia on memory functions [13]. In two studies, IR also has been associated with lower hippocampal volume [14,15], but this association was not found in a large dementia-free cohort [7]. Moreover, reduced amygdala volume has been related to higher fasting glycemia, but no association was found for the parahippocampal gyrus and the superior temporal gyrus volumes [9]. Finally, we are not aware of studies on the association between high GL diet and specific GM volumes.

Overall, the number of studies on the associations between glucometabolic changes and specific GM volumes are rare. Moreover, sample size was often small, and the populations under study and the specific GM volumes examined were heterogeneous. Therefore, we wanted to determine whether high GL diet and IR are associated with changes in GM volumes involved in the prodromal phase of dementia. First, we identified the GM volumes that were most related to prodromal dementia (diagnosed during the 7-year follow-up) using a data-driven machine learning algorithm. Then, we evaluated the association between GL diet, IR and these GM volumes.

## **METHODS**

### *Study participants*

The ESPRIT study is a longitudinal study of neuropsychiatric disorders in community-dwelling French older adults and part of the Three-City Study (a multicenter cohort study in three French cities: Bordeaux, Dijon and Montpellier) [16]. Eligible participants, aged 65 years and over and non-institutionalized, were recruited from the electoral rolls between 1999 and 2001. The University Hospital of Bicêtre (France) Ethics Committee approved the Three-City Study protocol, and all participants signed an informed consent. Interviews were carried out by nurses, psychologists, neurologists at baseline and after 2, 4, 7, 10, 12 and 15 years of follow-up. From the 1863 participants, only those younger than 80 years were invited for MRI; then, 760 participants were randomly selected among whom 668 had complete MRI volumetric data. At the 4-year follow-up visit, 549 participants completed a Food Frequency Questionnaire (FFQ) (n=119 participants were lost between baseline and the 4-year follow-up visit). Moreover, participants with missing data for intracranial volume (n = 10), fasting glycemia and fasting triglycerides (n = 2), GL (n = 22), and apolipoprotein E  $\epsilon$ 4 (*APOE- $\epsilon$ 4*) status (n = 4) also were excluded as well as participants with prevalent dementia (n = 4) and who developed incident dementia after the 7-year follow-up visit (n = 10; they were identified as cognitively normal during the first 7 years of follow-up). The final sample (n=497)

included 321 cognitively normal (CN) participants (i.e. subjects who remained cognitively normal during the 7 years of follow-up) and 176 participants with prodromal dementia (MCI/dementia) (i.e. subjects who developed MCI or dementia during the 7 years of follow-up).

#### *MRI and GM volume measurement*

Participants underwent MRI using the same scanner at the same examination center (Gui de Chauliac Neurology Hospital, Montpellier, France). A 1.5 T GE Signa Imaging system (General Electric Medical Systems, Milwaukee, WI) was used to acquire a contiguous AC-PC aligned axial IR-prepared SPGR T1-weighted sequence for volumetric estimations (TR=12, TE=2.8, IT=6000, matrix, size=256 ×256, pixel spacing=0.9375 ×0.9375 mm, NEX=1, slice thickness=1.0 mm). Regional reconstruction and segmentation were performed with the FreeSurfer 5.3 image analysis suite (<http://surfer.nmr.mgh.harvard.edu/>) as previously described [17]. For this study, 43 cortical and subcortical regions of interest (ROIs) were defined using the Desikan Atlas (sum of the left and right hemispheres) [18].

Using the segmentation tool of the SPM5 software (Wellcome Department of Cognitive Neurology, London, United Kingdom), the intracranial volume (gray + white matter + cerebrospinal fluid) was computed for each participant and was used as covariate in the models to minimize the effect due to global brain size differences.

#### *Glucometabolic indexes*

##### Glycemic load

GL is an indicator of the cumulative exposure to postprandial glycemia and reflects insulin demand, induced by the carbohydrate intake [19]. The total daily GL was calculated from the 148-item semi-quantitative FFQ, as described previously [6]. In the Bordeaux Three-City study, carbohydrate intake did not seem to change during the follow-up [20]. Thus, it was hypothesized that GL did not change from baseline to the follow-up visit in which the FFQ was filled in.

#### Triglyceride-Glucose (TyG) index

At baseline, fasting blood samples were collected to measure classical parameters, including fasting blood glucose (glycemia) and triglycerides. The TyG index has been proposed as a simple measure of IR. It was calculated as the  $\log(\text{fasting triglycerides} \times \text{fasting glucose}/2)$  and was expressed in  $\text{mg}^2/\text{dL}^2$  [21]. This index reflects both the lipotoxicity and glucotoxicity that play a crucial role in IR development [22]. It is strongly correlated with insulin sensitivity, measured with the euglycemic-hyperinsulinemic clamp ( $\rho = -0.68$ ) or the HOMA-IR ( $\rho = -0.77$ ) [23].

#### *Diagnosis of dementia and MCI*

According to the Paquid epidemiological study, a faster global cognitive decline seems to appear 7-8 years before the diagnosis of AD [24]. Therefore, for this study, a narrow time window of 7 years was chosen to identify with some confidence the brain structures related to prodromal dementia (MCI and participants with dementia). At the 2-, 4-, and 7-year follow-up visits, a neurologist examined all participants. Then, an independent committee of neurologists evaluated all potential cases of dementia to reach a consensus on the diagnosis and etiology based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [25]. Although the dementia type was determined during the clinical interview, for the present analysis, patients with AD and other dementia types were grouped together due to the low number of incident cases.

MCI can be considered as a dementia prodrome and was diagnosed according to the revised criteria for MCI (MCI-R algorithm), proposed by an international consensus group [26] and used elsewhere [27]. We also previously showed that the MCI-R algorithm allows a better prediction of the cognitive deficits that will progress towards dementia [28]. Briefly, MCI was diagnosed in the presence of a cognitive complaint and a score within the 20<sup>th</sup> percentile for the relevant age-matched and education-matched group in at least one of the neuropsychological cognitive tests used at baseline and during the 7-year follow-up (Benton Visual Retention Test, Isaacs' Set Test of verbal fluency, and

immediate and delayed recall of the Five-Word Test by Dubois and colleagues). The dementia or MCI onset date was the middle of the interval between the last follow-up without the event and the first follow-up with the event. Patients with MCI or with dementia were grouped (MCI/dementia) to account for slowly progressing dementia that may be diagnosed after the 7-year follow-up.

#### *Other variables*

Education level was defined as no school, primary school, high school, or graduate level. The Mini Mental State Examination [29] was used as an index of global cognitive performance. APOE genotyping was performed as previously described [30]. *APOE-ε4* carriers were defined as carrying at least one *ε4* allele. Energy intake was estimated from the FFQ as previously described [6]. Body mass index was calculated as weight (kg)/height<sup>2</sup> (m). Diabetes was defined as treated diabetes, fasting glycemia >7 mmol/L, and self-reported. History of stroke was established using standardized questions. Information was also obtained on alcohol consumption (no drinker/drinker), and smoking status (never, past, or current). Depressive symptomatology was evaluated with the Center for Epidemiological Studies-Depression scale [31], using the recommended French cut-off scores of 17 and 23 for significant depression in older men and women, respectively [32].

#### *Statistical analyses*

##### Selection of GM volumes related to MCI/dementia

To profile the GM volumes most related to MCI/dementia, the Random Forest algorithm implemented in the 'randomForest' R package was used [33]. The method is based on an ensemble of decision trees from which the prediction of a categorical variable (CN *versus* MCI/dementia) is obtained as the mean of the predicted values of all trees. This process, referred to as bagging, prevents model overfitting and generalizes well. At each node, Random Forest randomly selects a subset of variables to split. At each internal node, the best feature among a random subset of features is selected to maximize the reduction of label impurity. The process is recursively repeated

until the tree reaches a predefined depth, the number of samples in a node falls below a threshold, or all samples belong to the same class. First, the two main parameters were optimized using a grid search to improve the algorithm learning step. These two parameters are: *ntree* (the number of trees in the ensemble) and *mtry* (the number of variables randomly selected at each node). The following ranges were implemented: *ntree*, from 100 to 1000, and *mtry*, from 5 to 40. Both parameters were optimized for each tested fingerprint independently.

Second, the Random Forest algorithm was run with the optimized parameters (*ntree* = 700, and *mtry* = 20) and brain GM volume variables were chosen according to the mean decrease of the Gini index. The mean Gini index decrease is a concept of variable importance assessed by the Gini impurity metric. The Gini index is a measure of the prediction power of variables in classification, based on the principle of impurity reduction. It is non-parametric and thus, it does not rely on data belonging to a particular type of distribution.

### Main analysis

Linear regression was used to assess the association between glucometabolic indexes and the GM volumes identified by Random Forest. The model was adjusted for age, sex, education level, intracranial volume, *APOE-ε4* status, energy intake, tobacco, alcohol, depressive symptomatology, diabetes, and stroke history. As GL and energy intake are highly correlated, the residual method was used [34,35]. The effect modification by cognitive status (CN *versus* MCI/dementia group) was checked using interaction terms, and analyses were stratified according to the cognitive status. From the fitted linear models, predicted values of the GM volumes selected were calculated according to CN and MCI/dementia.

### Secondary analysis

To further explore asymmetrical associations, the same analyses were done separately for left and right hemisphere in the CN and MCI/dementia groups.

All statistical analyses were performed using R version 3.6.1.



## RESULTS

The participants' mean age at baseline was 71 years, and 51% were women (Table 1). During the 7 years of follow-up, MCI was diagnosed in 158 participants and dementia in 18 participants. Compared with the CN group (n=321), participants in the MCI/dementia group (n=176) were older and more likely to have had type 2 diabetes, stroke history, and depressive symptomatology.

### *GM volumes of the medial temporal region are the most related to MCI/dementia*

To select the GM volumes most related to MCI/dementia, a Random Forest algorithm was used to predict the participants' classification in the MCI/dementia group in function of their 43 brain volumes. The mean decrease of the Gini index revealed that the hippocampus (12.3), amygdala (10.0), caudate nucleus (9.6), temporal pole (9.4), putamen (8.0), and caudal anterior cingulate cortex (7.4) volumes contributed the most to the prediction of the MCI/dementia group (Figure 1). These results allowed defining the hippocampus, amygdala, caudate nucleus, temporal pole, putamen and caudal anterior cingulate cortex as the most important GM volumes related to MCI/dementia in our sample.

### *Glucometabolic changes are associated with reduced GM volumes in prodromal dementia*

To determine whether glucometabolic changes were associated with the selected GM volumes in prodromal dementia, first the interactions of these volumes with GL, TyG index, glycemia, and triglycerides were investigated in the two groups (CN and MCI/dementia). TyG index, glycemia, and triglycerides were significantly associated with the hippocampus and amygdala volumes in the MCI/dementia group (Figure 2 for the TyG index). Thus, the analysis was stratified by cognitive status.

In the CN group, only an association between higher glycemia and smaller putamen volume was found (Table 2, Supplementary Figure 1H).

In the MCI/dementia group, higher GL was significantly associated with reduced amygdala volumes after adjustment for age, sex, education level, intracranial volume, *APOE-ε4*, energy intake, tobacco, alcohol, depressive symptomatology, diabetes, stroke history (Table 2, Supplementary Figure 1B). Conversely, no significant association was found with the hippocampus, temporal pole, caudate nucleus, putamen and caudal anterior cingulate cortex volumes (Table 2). One-unit increase in the TyG index was associated with a 354 mm<sup>3</sup>, 291 mm<sup>3</sup>, and 520 mm<sup>3</sup> reduction of the hippocampus, amygdala, and putamen volume, respectively (Figure 2, Supplementary Figure 1A). Conversely, the TyG index was not associated with the caudate nucleus, temporal pole and caudal anterior cingulate cortex volumes. Higher glycemia was significantly associated with reduced temporal pole and caudal anterior cingulate cortex volumes (Supplementary Figure 1D and 1F), and tended to be associated with reduced hippocampal volume (Table 2). Finally, in the MCI/dementia group, one-unit increase in triglyceride concentration was associated with a 256 mm<sup>3</sup>, 217 mm<sup>3</sup>, and 393 mm<sup>3</sup> reduction of the hippocampus, amygdala, and putamen volume, respectively (Supplementary Figure 1C, 1E and 1G).

#### *Glucometabolic changes are associated with reduced GM volumes in both left and right hemisphere*

To explore asymmetrical associations, the same analyses were performed separately for the left and right hemisphere. In the CN group, glycemia and putamen volume were associated only in the left hemisphere (Supplementary Table 1). Moreover, high GL diet was significantly associated with lower right caudate nucleus volume.

In the MCI/dementia group, significant associations were observed in both hemispheres, particularly between TyG index and hippocampus, amygdala and putamen volumes (Supplementary Table 2). However, associations were stronger in the right hemisphere, with the exception of the association between GL diet and amygdala volume that was significant only in the left hemisphere.

These results showed that glucometabolic changes were associated with a decrease in the GM volumes of three (hippocampus, amygdala and putamen) of the regions most related to MCI/dementia.

## **DISCUSSION**

This study shows that brain GM volumes related to prodromal dementia (MCI/dementia) are associated with glucometabolic changes. In our sample, the hippocampus, amygdala, caudate nucleus, temporal pole, putamen, and caudal anterior cingulate cortex volumes were the most related to MCI/dementia diagnosed during the 7 years of follow-up. Moreover, the TyG index (a surrogate marker of IR) was associated with reduced hippocampal, amygdala and putamen volumes, and higher GL diet with reduced amygdala volume in the MCI/dementia group. Hippocampus, amygdala, caudate nucleus, temporal pole, putamen, and caudal anterior cingulate cortex volumes were the most related to MCI/dementia. Hippocampus, amygdala and temporal pole are part of the medial temporal lobe area that is the first region altered in AD [11]. In our sample, hippocampal and amygdala volumes were related to MCI/dementia detection during the first 7 years of follow-up, in agreement with other studies [11,36]. However, to our knowledge, no study has reported the association between temporal pole volume and MCI or dementia. The putamen and caudate nucleus are close to the medial temporal region. Previous studies already reported that putamen volume is decreased in patients with AD compared with patients with memory complaints [37], and that reduced caudate nucleus is associated with higher AD risk [38]. However, data on the caudate nucleus, temporal pole, putamen and caudal anterior cingulate cortex volumes are limited. As previous studies on the relationships between glucometabolic changes and GM volumes were mainly performed in cognitively healthy participants without dementia, cognitive impairment or diabetes, it is difficult to compare previous results with our findings. For example, IR has been

associated with lower hippocampal volume in 50 cognitively normal women [14], but not in the Framingham Offspring study [7]. However, in patients with AD, higher insulin levels after intravenous glucose tolerance test have been associated with lower hippocampal volume and greater atrophy of some GM regions of the putamen [8]. IR has been also associated with lower hippocampal volume and significantly reduced volumes in the temporal lobe area, specifically amygdala, putamen, temporal pole and caudate nucleus [15]. Overall, these studies are consistent with our results showing a significant association between TyG index and GM volumes in the MCI/dementia group, although we did not detect any significant association for temporal pole and caudate nucleus. We also found that higher fasting glycemia was associated with lower temporal pole and caudal anterior cingulate cortex volumes in the MCI/dementia group, however, we did not observe any significant association with hippocampus or amygdala volumes, unlike other studies [9,12,13]. Finally, we found that high GL diet was associated with lower amygdala volume in the MCI/dementia group and with the right caudate nucleus volume in the CN group, but not with hippocampus. On the other hand, a cross-sectional study showed that one or more servings of fruit juice per day were associated with lower hippocampal volume [39,40]. The GL considers all carbohydrate-based foods, not only free sugars and sugars added in beverages, and this may explain this disparity. Moreover, in children who usually eat bread (higher GL) at breakfast, caudate nucleus volume also was lower compared with those who eat rice (lower GL) [41]. Together, the previous and present findings suggest that both high GL diet and IR alter specific brain regions.

The absence of common associations of GL diet and TyG index with the hippocampus and putamen volumes suggests that these two glucometabolic parameters do not measure the same event. Indeed, GL estimates the mean postprandial glycemic and insulin responses, whereas the TyG index is designed to assess IR. Moreover, a person showing high glycemic and insulin responses does not necessarily develop IR, which may explain why GL and TyG index are not correlated. Specifically, the TyG index (measure of IR) was associated with reduced hippocampus, amygdala and putamen volumes in the MCI/dementia group. These regions are characterized by high density of insulin

receptors and may be more prone to IR than other brain regions [2,42]. A study showed that in normal conditions, insulin modulates glucose utilization in selective brain circuits. Conversely, in the presence of excessive hyperinsulinemia, the functional connectivity of the default mode network between the medial prefrontal cortex region and the parahippocampus and hippocampus was disrupted [43]. This study suggests that hyperinsulinemia contributes to impair synaptic connectivity. Moreover, IR impairs the glycolytic activity [44], and epidemiological studies demonstrated that IR is associated with brain glucose hypometabolism [45,46]. Brain glucose hypometabolism could be a marker of synaptic or neuronal injury. Indeed, insulin contributes to synaptogenesis and synaptic remodeling [2], and is involved in neuron survival regulation [47]. IR may prevent insulin from exerting its neuroprotective and neuromodulator effects in the brain. Thus, by altering the brain networks and glucose metabolism, IR could contribute to neurodegeneration and to the GM volume decrease of brain regions with high density of insulin receptors.

The main strengths of the present study include: the 1) large population-based sample for an MRI-based study, 2) data-driven Random Forest selection of brain volumes, that has important advantages over other techniques in terms of ability to handle non-linear data and robustness to noise, and 3) adjustment for many potential confounders, including age, sex, education, intracranial volume, *APOE-ε4* status, energy intake, tobacco, alcohol, depressive symptomatology, diabetes and stroke history. Among the potential limitations, the cross-sectional design of our study does not allow inferring about causality between glucometabolic changes and brain volumes alterations. Although our data may indicate a role of glucometabolic changes in GM volume alterations related to AD development, the possibility of "reverse causation" must be considered. Indeed, it has been shown that amyloid- $\beta$  aggregation impairs insulin signaling [48]. Moreover, brain regions that regulate insulin and food intake (e.g. hypothalamus) can be altered in AD pathology [49], leading to systemic insulin dysregulation. Thus, glucometabolic changes may be the result of AD effects on GM volumes. Finally, it would have been important to differentiate GM alterations linked to AD and to MCI by studying the dementia and MCI groups separately. However, this was not possible due to the

lack of statistical power. In addition, in the MCI group, some participants may develop dementia, but we did not have this information. Our findings suggest that targeting the glucometabolic control early in life to prevent brain alterations might contribute to slow down and prevent the development of cognitive impairment and dementia later in life.

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## Disclosure statement

The authors have no conflict of interest to report

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Table 1. Characteristics of the study population

Characteristics Mean (SD) or n (%)	Whole sample n = 497	CN n = 321	MCI/dementia n = 176	P value
Age (years)	71.0 (3.9)	70.4 (3.8)	72.1 (4.0)	<b>&lt;.0001</b>
Women	255 (51.3)	177 (55.1)	78 (44.3)	<b>0.0268</b>
Education level				0.8162
No school	123 (24.7)	77 (24.0)	46 (26.1)	
Primary school	134 (27.0)	90 (28.0)	44 (25.0)	
High school	92 (18.5)	57 (17.8)	35 (19.9)	
Graduated	148 (29.8)	97 (30.2)	51 (29.0)	
MMSE (IQR)	27.7 (1.8)	27.8 (1.6)	27.4 (1.9)	<b>0.0045</b>
<i>APOE</i> - $\epsilon$ 4 carriers	99 (19.9)	58 (18.1)	41 (23.3)	0.2013
BMI (kg/m <sup>2</sup> )	25.0 (3.3)	25.1 (3.3)	24.8 (3.3)	0.4666
Alcohol use	419 (84.3)	269 (83.8)	150 (85.2)	0.5646
Tobacco use	226 (45.5)	146 (45.5)	80 (45.5)	1
Type 2 diabetes	52 (10.5)	25 (7.8)	27 (15.3)	<b>0.0132</b>
Stroke history	21 (4.2)	8 (2.5)	13 (7.4)	<b>0.0186</b>
Depressive symptomatology	52 (10.5)	22 (6.9)	30 (17.0)	<b>0.0006</b>
Energy intake (kcal/day)	1267 (432)	1244 (394)	1309 (492)	0.1084
Glycemic load (/day)	116 (39.2)	114 (35.9)	118 (44.5)	0.2746
Glycemic load residuals (/day)	0 (15.0)	0.5 (14.6)	-0.9 (15.6)	0.3066
Glycemia (mol/L)	5.07 (1.05)	4.98 (0.82)	5.23 (1.36)	<b>0.011</b>
Triglycerides (mol/L)	1.26 (0.61)	1.26 (0.63)	1.26 (0.58)	0.9665
TyG index (mg <sup>2</sup> /dL <sup>2</sup> )	8.42 (0.48)	8.41 (0.47)	8.45 (0.50)	0.7059

Abbreviations: *APOE*- $\epsilon$ 4, apolipoprotein E  $\epsilon$ 4 allele; BMI, body mass index; CN, cognitively normal;

IQR, interquartile range; MCI, Mild Cognitive Impairment; MMSE, Mini Mental State Examination; SD, standard deviation; TyG, Triglycerides-Glucose.

Table 2. Association between GL, TyG index, glycemia, triglycerides and Random Forest-selected GM volumes stratified in function of the cognitive status.

Exposures	Hippocampus		Amygdala		Caudate nucleus		Temporal pole		Putamen		Caudal anterior cingulate	
	$\beta$ (SE)	<i>P</i> value	$\beta$ (SE)	<i>P</i> value	$\beta$ (SE)	<i>P</i> value	$\beta$ (SE)	<i>P</i> value	$\beta$ (SE)	<i>P</i> value	$\beta$ (SE)	<i>P</i> value
<u>Cognitively normal during the follow-up (n = 321)</u>												
GL	-7.63(29.9)	0.7988	-17.8(13.2)	0.1794	-58.5(33.9)	0.0856	12.5(29.3)	0.6698	-8.81(45.2)	0.8458	13.7(22.9)	0.55
TyG index	-41.4(93.1)	0.6567	31.1(41.3)	0.4517	-9.0(106)	0.9321	91.5(91.1)	0.3159	-142(141)	0.3119	-40.7(71.3)	0.5689
Glycemia	-32.6(63.2)	0.6061	-12.2(28.0)	0.6633	-44.1(71.9)	0.54	-31.0(61.8)	0.6162	-195(95.1)	<b>0.0414</b>	-4.70(48.4)	0.9222
Triglycerides	-20.4(67.0)	0.761	24.1(29.7)	0.418	15.6(76.3)	0.8381	118(65.3)	0.0707	2.80(102)	0.9783	-53.4(51.2)	0.2979
<u>MCI/dementia during the follow-up (n = 176)</u>												
GL	-54.0(44.1)	0.2222	-46.4(22.2)	<b>0.0381</b>	-85.6(55.2)	0.123	-53.3(43.4)	0.2205	-39.1(63.1)	0.5366	-22.5(28.8)	0.4356
TyG index	-354(146)	<b>0.0168</b>	-291(72.0)	<b>0.0001</b>	-130(187)	0.4895	-208(146)	0.156	-520(209)	<b>0.0137</b>	-163(96.2)	0.0921
Glycemia	-129(69.3)	0.0637	-56.9(35.3)	0.1088	-105(87.7)	0.2316	-154(67.9)	<b>0.0245</b>	-106(99.6)	0.2887	-105(44.9)	<b>0.0203</b>
Triglycerides	-256(116.5)	<b>0.0297</b>	-217(57.5)	<b>0.0002</b>	-62.5(149)	0.6747	-59.2(116)	0.6116	-393(166)	<b>0.019</b>	-118(76.5)	0.1257

Linear model adjusted for age, sex, education, intracranial volume, *APOE-ε4*, energy intake, tobacco, alcohol, depressive symptomatology, diabetes, stroke history.

Abbreviations: GL, glycemic load; MCI, Mild Cognitive Impairment; SE, standard error; TyG, Triglycerides-Glucose; GM, Gray Matter

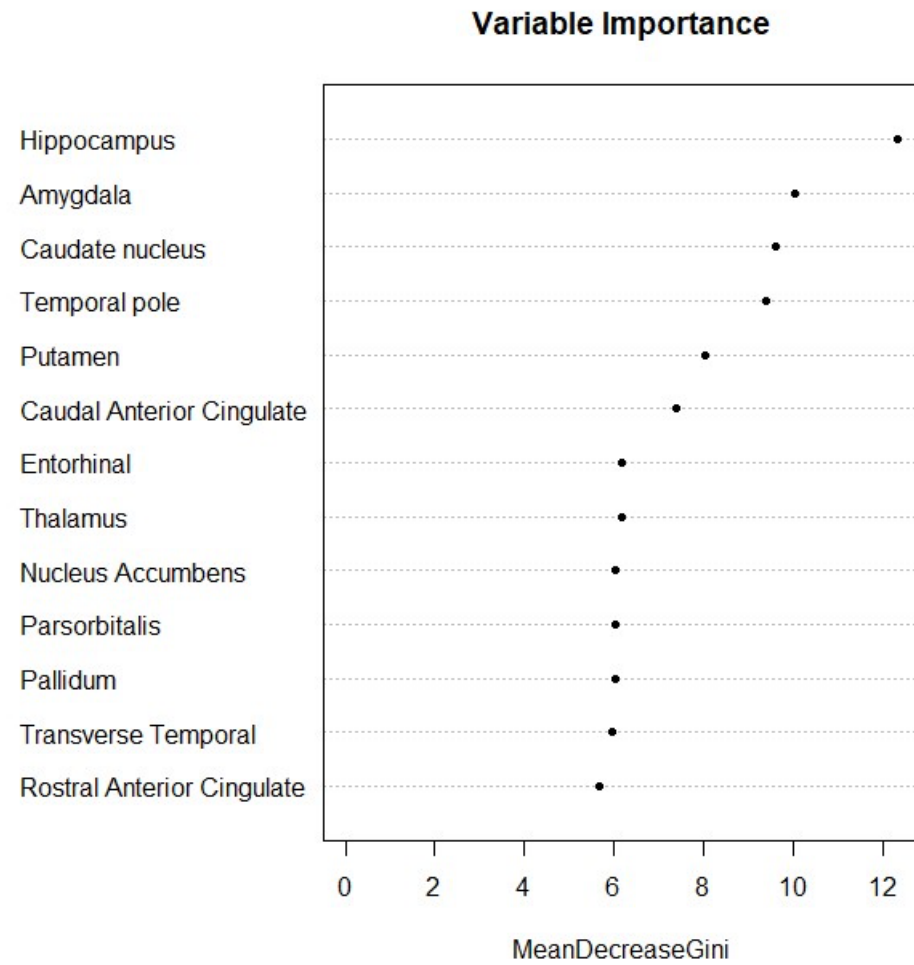


Figure 1. Gray matter (GM) volume importance for predicting MCI/dementia. The figure shows the most relevant brain regions for MCI/dementia detection based on the mean decrease of the Gini index.

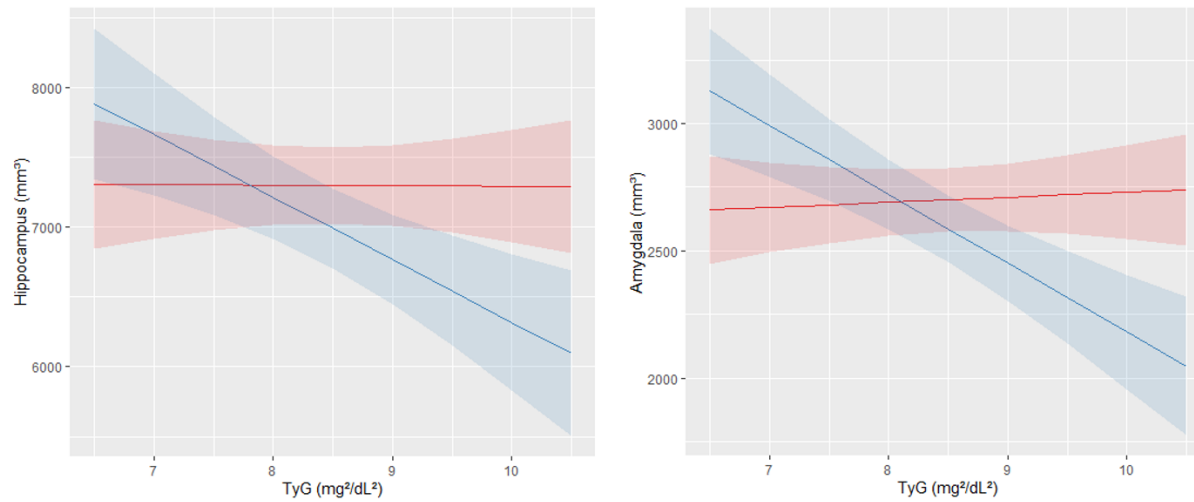


Figure 2. Predicted values of hippocampal volume and amygdala volume in function of the TyG index according to the cognitive status. Predicted values of hippocampal volume are on the left and those of amygdala volume on the right. Red line represented cognitively normal group and blue line MCI/dementia group.

Supplementary Table 1. Association between GL, TyG index, glycemia, triglycerides and Random Forest-selected GM volumes in the left and right hemisphere in the **cognitively normal** group (n = 321).

Exposures	Hippocampus		Amygdala		Caudate nucleus		Temporal pole		Putamen		Caudal anterior cingulate	
	$\beta$ (SE)	P value	$\beta$ (SE)	P value	$\beta$ (SE)	P value	$\beta$ (SE)	P value	$\beta$ (SE)	P value	$\beta$ (SE)	P value
<u>Left Hemisphere</u>												
GL	-6.2(16.8)	0.7118	-3.49(7.51)	0.642	-17.9(17.0)	0.2934	-5.09(18.4)	0.7823	3.08(25.1)	0.9025	5.03(14.6)	0.7312
TyG index	8.6(52.2)	0.8688	21.6(23.3)	0.3558	10.1(53.2)	0.8499	49.2(57.2)	0.3908	-69.1(78.0)	0.3761	23.7(45.5)	0.6038
Glycemia	-18.2(35.4)	0.6072	-10.1(15.8)	0.5232	-9.20(36.0)	0.7991	-1.80(38.8)	0.9623	-108(52.6)	<b>0.0414</b>	0.70(30.9)	0.9824
Triglycerides	6.1(37.5)	0.8718	21.2(16.8)	0.2079	15.4(38.2)	0.6873	66.7(41)	0.1047	1.80(56.1)	0.9745	6.40(32.7)	0.845
<u>Right Hemisphere</u>												
GL	-1.43(15.5)	0.9266	-14.3(7.68)	0.0634	-40.6(18.0)	<b>0.0248</b>	17.6(17.4)	0.3122	-11.9(23.4)	0.6114	8.68(15.9)	0.5852
TyG index	-50.0(48.3)	0.301	9.50(24.0)	0.6928	-19.1(56.5)	0.7351	42.3(54.2)	0.435	-73.3(72.6)	0.3137	-64.3(49.4)	0.1935
Glycemia	-10.6(32.8)	0.7473	-1.40(16.3)	0.934	-35.4(38.2)	0.3558	-30.0(36.7)	0.4148	-82.3(49.1)	0.0949	-5.4(33.6)	0.8724
Triglycerides	-28.9(34.7)	0.4057	2.40(17.3)	0.8896	0.50(40.6)	0.9904	51.8(38.9)	0.1833	-1.50(52.3)	0.9766	-59.8(35.4)	0.0924

Linear model adjusted for age, sex, education level, intracranial volume, *APOE- $\epsilon$ 4*, energy intake, tobacco, alcohol, depressive symptomatology, diabetes, stroke history.

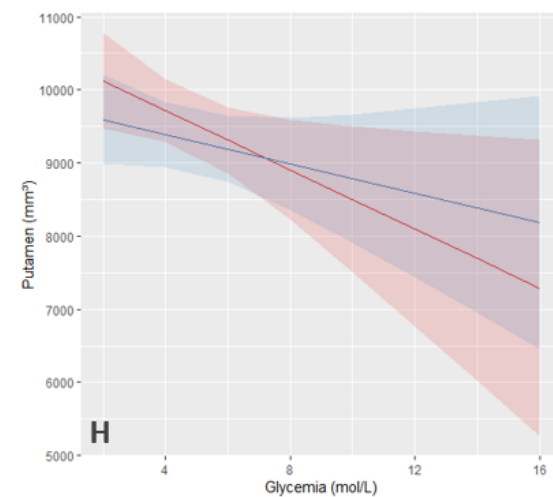
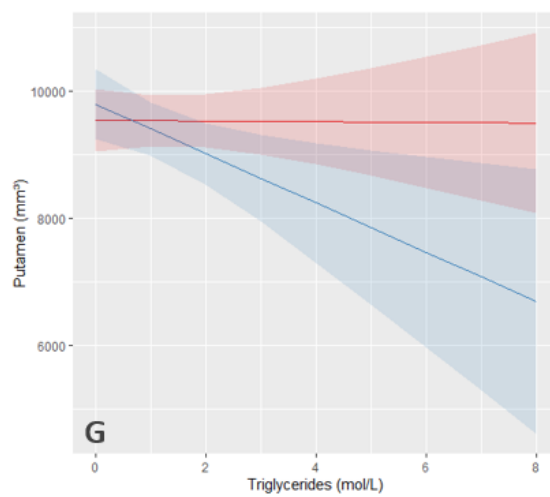
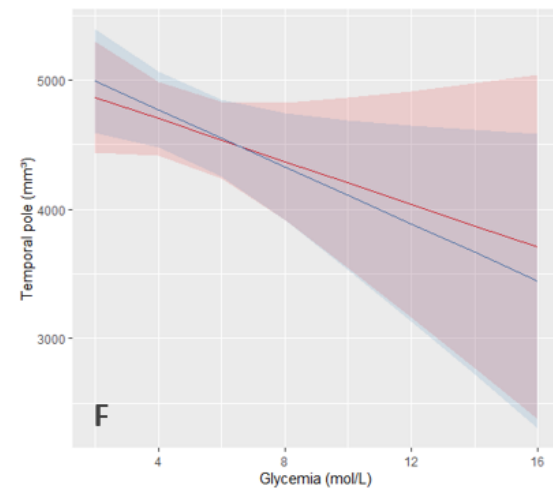
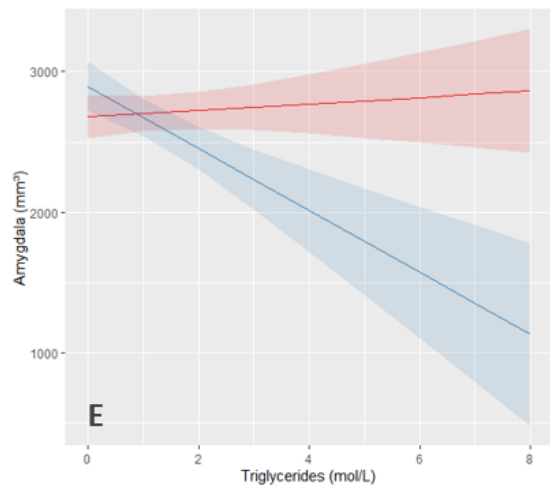
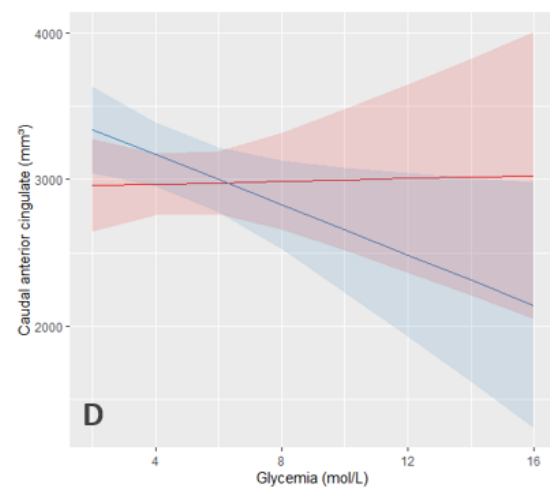
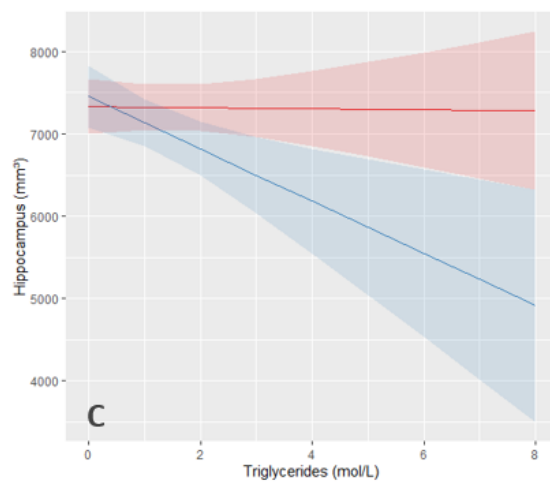
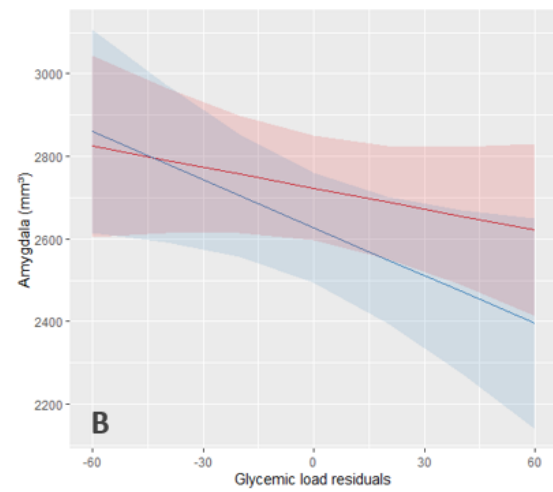
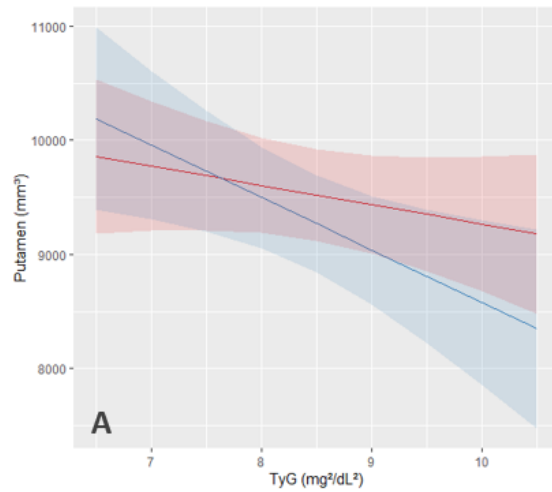
Key: GL, glycemic load; SE, standard error; TyG, Triglycerides-Glucose; GM, Gray Matter.

Supplementary Table 2. Association between GL, TyG index, glycemia, triglycerides and Random Forest-selected GM volumes in the left and right hemisphere in the **MCI/dementia** group (n = 176).

Exposures	Hippocampus		Amygdala		Caudate nucleus		Temporal pole		Putamen		Caudal anterior cingulate	
	$\beta$ (SE)	P value	$\beta$ (SE)	P value	$\beta$ (SE)	P value	$\beta$ (SE)	P value	$\beta$ (SE)	P value	$\beta$ (SE)	P value
<u>Left Hemisphere</u>												
GL	-25.7(25.49)	0.3149	-23.4(11.5)	<b>0.0428</b>	-39.7(27.6)	0.1524	-43.5(25.1)	0.0856	-6.60(31.8)	0.8359	-9.89(20.3)	0.627
TyG index	-166.4(85.1)	<b>0.0522</b>	-138.5(37.5)	<b>0.0004</b>	-89.1(93.3)	0.3409	-78.5(85.2)	0.3583	-254(105)	<b>0.0171</b>	-58.2(68.3)	0.3954
Glycemia	-69.4(40.1)	0.0856	-29.1(18.3)	0.1131	-59.9(43.7)	0.1723	-67.1(39.8)	0.0938	-54.7(50.2)	0.2774	-54.8(31.9)	0.0876
Triglycerides	-115.9(67.7)	0.0891	-99.2(30.1)	<b>0.0012</b>	-38.7(74.2)	0.6027	-27.0(67.8)	0.6905	-185(83.8)	<b>0.0285</b>	-46.8(54.2)	0.3892
<u>Right Hemisphere</u>												
GL	-28.3(21.3)	0.1854	-22.9(12.4)	0.0674	-45.9(29.0)	0.1155	-9.83(25.1)	0.6956	-32.5(34.5)	0.3489	-12.6(19.4)	0.5165
TyG index	-187(70.4)	<b>0.0086</b>	-152.1(40.5)	<b>0.0002</b>	-40.5(98.4)	0.6814	-129(83.9)	0.1254	-266(115)	<b>0.0217</b>	-105(64.7)	0.1076
Glycemia	-60.0(33.5)	0.0753	-27.8(19.8)	0.1618	-45.3(46.2)	0.3275	-87(39.1)	<b>0.0276</b>	-51.3(54.7)	0.3495	-50.3(30.4)	0.1003
Triglycerides	-139.7(56.1)	<b>0.0137</b>	-118.2(32.2)	<b>0.0003</b>	-23.8(78.2)	0.7611	-32.2(67)	0.6322	-208(91.1)	<b>0.0239</b>	-70.9(51.5)	0.1706

Linear model adjusted for age, sex, education level, intracranial volume, *APOE- $\epsilon$ 4*, energy intake, tobacco, alcohol, depressive symptomatology, diabetes, stroke history.

Key: GL, glycemic load; SE, standard error; TyG, Triglycerides-Glucose, GM, Gray matter.





2     Supplementary Figure 1. Predicted values of GM volume in function of the GL, TyG index, glycemia or  
3     triglycerides according to the cognitive status. Red line represented cognitively normal group and  
4     blue line MCI/dementia group. (A) Predicted values of putamen volume in function of the TyG index.  
5     (B) Predicted values of amygdala volume in function of the GL. (C) Predicted values of hippocampal  
6     volume in function of the triglycerides. (D) Predicted values of caudal anterior cingulate cortex  
7     volume in function of the glycemia. (E) Predicted values of amygdala volume in function of the  
8     triglycerides. (F) Predicted values of temporal pole volume in function of the glycemia (G) Predicted  
9     values of putamen volume in function of the triglycerides. (H) Predicted values of putamen volume in  
10    function of the glycemia.

11