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► To cite this version:

Léonard Guillou, Valérie Durand, Michel Raymond, Claire Berticat. Chronic refined carbohydrate consumption measured by glycemic load and variation in cognitive performance in healthy people. *Personality and Individual Differences*, 2023, 206, pp.112138. 10.1016/j.paid.2023.112138. hal-04016630

HAL Id: hal-04016630

<https://hal.science/hal-04016630v1>

Submitted on 6 Mar 2023

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**Chronic refined carbohydrate consumption measured by glycemic load
and variation in cognitive performance in healthy people**

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30 **Abstract**

31

32 A massive diet switch has occurred in the occidental world since the second half of the 20th century, with a
33 dramatic increase in refined carbohydrate consumption generating numerous deleterious health effects. Physiological
34 mechanisms associated with refined carbohydrate consumption, such as hyperinsulinemia and insulin resistance, may
35 impact cognition in healthy people before overt obesity, metabolic disease onset or dementia. To explore this
36 possibility, the relationship between cognitive performance and chronic refined carbohydrate consumption was
37 studied in healthy young adults (N = 95). Evaluation of chronic refined consumption was based on the glycemic load
38 (a proxy of glycemic and insulinemic responses) of three mealtimes at higher glycemic risk: breakfast, afternoon
39 snacking and between-meal snacking. Immediate consumption of refined carbohydrates was experimentally
40 controlled. High chronic between-meal glycemic load is associated to a decrease of cognitive performance for men
41 and women in the presence of several control variables, including energy intake. The different physiological ecologies
42 of the three meals and the interpretation of the results in terms of adaptation or maladaptation to the modern dietary
43 environment are discussed.

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47 **Key Words**

48 Refined carbohydrates, diet evolution, cognition, sugars, high glycemic load, energy intake

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54 **1. Introduction**

55

56 Each animal species is adapted to a specific diet (carnivore, herbivore, etc.) through a more or less specialized
57 digestive process. Usually, a sudden and drastic change in diet leads to health problems due to inadequate nutrition,
58 revealing that the change has driven the population outside of their adaptive peak.

59 For most Western people, substantial diet changes have occurred during the second half of the 20th century,
60 although some changes began earlier in the century. Industrialized foods were developed, with the introduction of
61 highly processed refined products, in particular refined carbohydrates (primary sucrose, fiber-depleted gelatinous
62 starches, high sugar corn syrup, and sugars; Cordain et al., 2005). This massive dietary change has been associated
63 with various medical problems, such as obesity, insulin resistance, type II diabetes, cardiovascular diseases, myopia,
64 dental caries, Alzheimer's disease, hypertension, inflammatory diseases, and cancer. (Carrera-Bastos et al., 2011;
65 Craft, 2007; Gentreau et al., 2020; Jellinger, 2007; Lustig et al., 2012; Myles, 2014; Sofi et al., 2008, 2010; Thorburn
66 et al., 2014). The physiological mechanisms involved in these pathologies are now thought to involve in particular
67 repeated hyperglycemia/hyperinsulinemia and insulin resistance caused by the overconsumption of refined
68 carbohydrates (Cordain et al., 2003, 2005). Insulin resistance is defined as an impaired biologic response to insulin
69 stimulation of target tissues, primarily liver, muscle, and adipose tissue, but also brain.

70 Insulin has a pivotal function in the brain. Insulin signaling not only regulates energy metabolism, cell
71 survival, and cellular homeostasis but also has a neuroprotective role, regulates the concentration of several
72 neurotransmitters and supports neuronal plasticity (Y. Sun et al., 2020). Consequently, insulin resistance may directly
73 impact cognition, as shown by the association between insulin resistance (and high glycemia) and cognitive
74 impairment (e.g., orientation, concentration and memory) and increased risk of dementia (e.g., Neergaard et al., 2017;
75 Willette et al., 2015). Chronic consumption of refined carbohydrates could therefore also promote cognitive
76 impairment via insulin resistance. In obese individuals, often characterized by long-term consumption of high
77 glycemic load meals and insulin resistance, reduced memory and executive functioning have been consistently
78 demonstrated (Gunstad et al., 2006). In adults with type 2 diabetes, also characterized by long-term consumption of
79 high glycemic load meals and insulin resistance, it was demonstrated that the degree of glycemic control was related
80 to cognitive performance (Greenwood et al. 2003). In older people, high refined carbohydrate diets have recently been

81 identified as a potential risk factor for Alzheimer's disease and cognitive impairment, with an underlying hypothesis
82 involving the influence of insulin resistance (Gentreau et al., 2020). Poor vascularization of the brain due to
83 degradation of the capillary network by chronic hyperglycemia has also been proposed to explain this phenomenon
84 (Shigaeff et al., 2012). Additionally, damage from cardiovascular disease, one of the main risk factor of which is
85 chronic high glycemic load diet (Jenkins et al. 2021), may also contribute to cognitive decline (Deckers et al. 2017;
86 Eggermont et al. 2012). Immediate refined carbohydrate consumption could also affect cognitive performance through
87 blood glucose levels (Greenwood et al. 2003, Papanikolaou et al. 2006, Young & Benton, 2014). Particularly, it has
88 been shown that the way carbohydrates raise blood glucose levels during breakfast may influence the cognitive
89 performance of participants (Edefonti et al., 2017; Ingwersen et al., 2007).

90 To date, studies on the link between the long-term consumption of refined carbohydrates and cognition have
91 mainly been carried out on older individuals or in a pathological context. Nevertheless, early life exposure to refined
92 carbohydrates (i.e., prenatal, juvenile, and adolescence periods) may be particularly toxic to cognitive functioning, and
93 neurocognitive deficits induced by a diet high in refined carbohydrates may manifest before overt obesity or metabolic
94 disease onset (for a review see Hawkins et al., 2018). Here, we investigated whether refined carbohydrate
95 consumption affects cognition in healthy young adults, men and women, taking into account several confounding
96 variables and experimentally controlling for immediate carbohydrate consumption. Evaluation of refined carbohydrate
97 consumption was based on the total glycemic load (a proxy of glycemic and insulinemic responses) of three
98 mealtimes at higher glycemic risk (breakfast, afternoon snack and between-meal snack). Subjects were given an
99 isocaloric high or low glycemia breakfast, they responded to a diet questionnaire and, at three different defined times,
100 they performed a cognitive test, and their blood glucose was measured. We were thus able to address how chronic
101 refined carbohydrate consumption can affect cognition in healthy adults.

102

103

104 **2. Methods**

105

106 **2.1. Participants**

107 Individuals between 20 and 30 years of age were recruited at the University of Montpellier, France, through
108 an online form. The inclusion criteria used to participate in this experiment were the health status (nondiabetic,
109 without food allergies) and the diet habit (usually eating breakfast). In addition, to limit cultural heterogeneity, only
110 individuals declaring European ancestry were retained (95 participants: 48 female and 47 male).

111

112 **2.2. Experimental design**

113 The participants came in groups of three or four (one group/day) to the laboratory early in the morning and
114 followed the procedure described below. At baseline (step 1), subject glycemia was measured (G1). Glycemia was
115 read by a glucose meter (ACCU-CHEK Performa Nano Roche) into which a strip with a blood drop was inserted.
116 Blood drops were obtained with a single-use lancing pen that was self-operated by each subject. Then, they completed
117 the Wechsler's digit symbol substitution cognitive test (Wechsler, 1981). This test is sensitive to dementia, cortical
118 damage and cognitive changes. It makes it possible to assess visual-motor coordination, mental and motor speed,
119 executive functions and attention (Hugonot-Diener et al., 2008). Immediately following the test, one of two types of
120 isocaloric breakfasts (500 kcal), B1 and B2, randomly chosen each day, was served to the whole group. B1 was
121 composed of nonrefined carbohydrates (stone-ground wholemeal bread, butter, cheese, a raw fruit -orange or apple-
122 and a nonsweetened beverage -coffee, tea- without sugar available) and B2 was composed of refined carbohydrates
123 (French baguette made from industrially milled flour, jam, fruit juice -orange or apple- and a nonsweetened beverage -
124 coffee, tea- with sugar available). Once participants finished their breakfast, they completed a personal questionnaire
125 and a quantitative diet questionnaire. Half an hour after the end of breakfast (step 2) and one and a half hours after
126 breakfast (step 3), the participants' glycemia was again measured, and they undertook the Wechsler cognitive test.
127 Between step 2 and step 3, several morphometric variables (weight and height) were measured. Tests and
128 questionnaires were completed on an online interface developed with PHP, HTML, MySQL and JavaScript. Time was
129 recorded at each step, with $t = 0$ minutes at the first Wechsler's test. Over the two months of experimentation,
130 breakfast B1 was served as many times as breakfast B2.

131

132 **2.3. Cognitive test**

133 A computer version of Wechsler’s digit symbol substitution test was administered to participants
134 (Supplementary Figure S1). This test has been validated in the WAIS-III (Wechsler Adult Intelligence Scale) with a
135 sample of 1200 participants from 16 to 89 years (Ryan & Lopez, 2001). A list of 9 digit-symbol pairs (association
136 rule) was displayed on the top of the screen. Below, a random digit was displayed with all the symbols in a random
137 order. The participant had to click on the correct symbol corresponding to the displayed digit, according to the
138 association rule above. The goal was to correctly associate as many symbols as possible with their corresponding digit
139 during the allocated time (approximately 2 minutes). The number of correct clicks (CC; according to the specific
140 association rule displayed on the screen) during the allocated time was recorded. To avoid learning effects, digit-
141 symbol association rules were randomly changed between each test session.

142

143 **2.4. Questionnaires**

144 The personal questionnaire was used to collect possible confounding variables potentially affecting cognitive
145 performance and diet: sex, age, socioeconomic status (parents homeowners, yes: 1, no: 0), and physical activity level
146 (0 to 5).

147 The quantitative diet questionnaire concerning for breakfast, afternoon snack [“goûter” in French,
148 corresponding to an after-school snack] and between-meals snack of the day before (Slimani et al., 2000) was used to
149 estimate participants’ chronic refined carbohydrate consumption. The various daily meals have different nutritional
150 compositions, and thus do not bring the same glycemic response. Indeed, carbohydrates are rarely ingested alone, and
151 their degradation and absorption rates during digestion are modified by the other macronutrients. The glycemic
152 response will be higher with a meal rich in refined carbohydrates and poor in fat, protein and fiber (Hätönen et al.,
153 2011; L. Sun et al., 2020). Moreover, the order of food macronutrient intake also changes glycemic and insulinemic
154 responses (L. Sun et al., 2020). As a consequence, meals such as breakfast, afternoon snacks and between-meal snacks
155 may be at higher glycemic risk than other meals because they are described as richer in refined carbohydrates and
156 contain fewer food items (Bellisle, 2014; Bellisle et al., 2003, 2018). For each of these three meals, participants had to
157 identify the foods consumed from a list of proposed items (Table S1) and their corresponding serving-size using the
158 SU.VI.MAX cohort portion book, which allows an accurate estimation of the quantity consumed for each food with

159 photos indicating several possible sizes (Hercberg et al., 2004). The different food groups chronically consumed
160 during these 3 meals are shown in Table 1.

161

162 **2.5. Daily Diet Variables**

163 For each food item in the diet questionnaires, the glycemic index (GI) was calculated according to the
164 International Tables of glycemic Index (Foster-Powell et al., 2002) and internet updates (www.glycemicindex.com),
165 using glucose as the reference. The GI refers to the rate of glucose release by measuring the 2 h postprandial glycemia
166 value after consumption of a food portion containing 50 g of available carbohydrates relative to 50 g of glucose
167 consumption. Glycemic load (GL) reflects both carbohydrate quantity and quality. Compared with low-GL diets, high-
168 GL diets elicit larger glycemic and insulinemic responses (Foster-Powell et al., 2002). For each participant and each
169 item, GL was calculated by multiplying the GI by the amount of available carbohydrates (g) per serving estimated
170 from the photographs of SU.VI.MAX cohort catalog, divided by 100 (Monro & Shaw, 2008). Foods with low
171 carbohydrate content (e.g., meat, fats) were not assigned any glycemic load value (Bakel et al., 2009). For each
172 subject, the glycemic load for each item was summed, leading to a total glycemic load (Table 2) estimation for
173 breakfast (GL1), afternoon snack (GL2) and between-meal intake (GL3).

174 Energy intake (EI) and macronutrients for each item were obtained from the Anses-Ciqual database
175 (www.anses.ciqua.fr) and were calculated for each participant depending on the corresponding serving size estimated
176 from the SU.VI.MAX cohort catalog. For each subject, they were summed, resulting in a total energy intake
177 estimation for breakfast (EI1), afternoon snack (EI2) and between-meal intake (EI3), and corresponding macronutrient
178 compositions (Table 2).

179 To measure GL independently of EI, linear models were used to produce regressions of EI as a function of
180 GL for each meal (lm function from the R stats package version 3.6.3). These regression residuals were then used as
181 new variables (Willett et al., 1997). In this way, each subject's refined residual carbohydrate consumption was
182 described for breakfast (RGL1), afternoon snack (RGL2) and between-meal intake (RGL3). These variables represent
183 the glycemic load part of food that is not explained by energy intake.

184

185 **2.6. Statistical Analyses**

186 2.6.1. Effects of immediate breakfast consumption on glycemia.

187 To assess the effect of breakfast type on glycemia, G1, G2 and G3 were compared across the B1 and B2
188 breakfast types (Table 3). At baseline (before breakfast), no significant difference in G1 glycemia was found between
189 B1 and B2 (Wilcoxon-Mann-Whitney, $P = 0.66$). However, glycemia following breakfast (G2 and G3) was
190 significantly different between B1 and B2 (Wilcoxon-Mann-Whitney: $P < 10^{-7}$ for G2, and $P = 0.04$ for G3).
191 Consumption of refined carbohydrates during breakfast thus had a significant immediate effect on glycemia (Figure
192 1).

193 2.6.2. Statistical analyses for cognitive performance.

194 Linear mixed models were used to analyze cognitive performance in relation to the chronic refined
195 carbohydrate glycemic load of the three meals. The response variable was the number of correct clicks (CC). Subjects
196 completed the same cognitive test several times, and so participant was a random-effect variable. The maximum
197 random effects structure (intercept and slope) was included according to (Barr et al., 2013). RGL1, RGL2 and RGL3
198 were integrated into the model as the variables of interest, and several control variables potentially affecting cognitive
199 performance and diet were added: the type of breakfast served (B1 or B2), energy intake (EI1, EI2 and EI3), a
200 quadratic effect of time since the first test (t and t^2), sex, age, BMI (calculated as weight divided by the squared
201 height; Craft, 2007; Kim & Feldman, 2015), parents' homeowner status and physical activity level (Donnelly et al.,
202 2016; Mikus et al., 2012). Interactions with sex were included in the model. $P < 0.10$ was considered statistically
203 significant for interaction terms.

204 All statistical analyses were performed using R software version 3.6.3 using the package lme4 (v1.1-26;
205 Bates et al., 2015). All quantitative variables used in the models were centered and scaled. The significance of each
206 term was assessed from the model including all of the other variables. The variance inflation factor was computed
207 using the vif.mer function adapted from the vif function of the R package rms (v6.2-0; Harrell, 2015; Zuur et al.,
208 2010).

209

210 **2.7. Ethical Statement**

211 The protocol used to recruit participants and collect data was approved by the French Committee of
212 Information and Liberty (CNIL #1783997V0) and the Committee for the protection of persons (CPP IDRCB 2018-

213 A00505-50). For each participant, the general purpose of the study was explained (“Effects of diet on major
214 phenotypic traits”), and a written voluntary agreement was obtained for a statistical use of data (private information).
215 Data were analyzed anonymously.

216

217

218 **3. Results**

219

220 Descriptive statistics of the physical characteristics of the 95 participants (48 female and 47 male) are given
221 in Table 4. The proportions of individuals eating an afternoon snack were 40% and 54% for males and females,
222 respectively, and those eating a between-meal snack were 25% for both sexes (Table 1). Mean glycemic load (GL) and
223 energy intake (EI) for each meal are indicated in Table 2. GL items are defined as “low” when the GL value is below
224 10 and as “high” when the value is above 20 (Eleazu, 2016). GL values were within the same range of variation as
225 those from other studies on the French population (Berticat et al., 2020; Gentreau et al., 2022).

226 Chronic refined carbohydrate consumption, chronic energy intake and the other control variables had different
227 effects on cognitive performance (Table 5). Only the interaction term between sex and BMI had a *P*-value under the
228 threshold of 0.10 and was thus kept in the final model. Between-meal refined carbohydrate consumption significantly
229 decreased cognitive performance (RGL3, $\beta = -1.64$, $se = 0.71$, $P = 0.02$). Cognitive performance was also
230 significantly affected by energy intake at the afternoon snack (EI2, $\beta = -1.46$, $se = 0.71$, $P = 0.04$), and a trend in the
231 same direction was observed for energy intake at breakfast (EI1, $\beta = -1.15$, $se = 0.66$, $P = 0.08$). No effect of
232 immediate breakfast on cognitive performance was detected ($P = 0.67$). A significant negative effect of BMI ($\beta = -$
233 3.04 , $se = 0.89$, $P = 0.004$) was observed which appeared to be mainly driven by men (BMI.sex, $\beta = 2.75$, $se = 1.53$, P
234 $= 0.07$; β men = -3.04 ; β women = -0.29). The linear and quadratic effects of time were both statistically significant
235 (both $P < 10^{-11}$). The performance of individuals on Wechsler’s digit symbol substitution test improved over time (t , β
236 $= 6.35$, $se = 0.60$, $P < 10^{-15}$), as expected, due to habituation of the participants, although the association rules were
237 changed between each test session. All other variables studied were nonsignificant. Removing an outlier for GL3

238 variable from initial dataset (GL3 = 110, greater than 2 standard deviations from mean, Table 2) did not qualitatively
239 change the results.

240 The full model explained 31% of the total variance. The variance inflation factors (VIFs) were less than 1.9
241 (except for the related variables, time and squared time). The VIF values indicated that the multicollinearity between
242 covariables was weak and not of concern (Zuur et al., 2010).

243

244

245 **4. Discussion**

246

247 In this study, we investigated whether chronic refined carbohydrate consumption estimated by the glycemic
248 load of three mealtimes at higher glycemic risk (breakfast, afternoon snack and between-meal snack) was related to
249 cognitive performance in healthy women and men. We found that cognitive performance as measured by Wechsler's
250 digit symbol substitution test was not independent of chronic between-meals consumption of refined carbohydrates.
251 The higher the consumption of refined carbohydrates between meals, the lower the cognitive performance. This effect
252 was maintained when controlling for potential confounding effects such as age, sex, BMI, physical activity, parental
253 home ownership, chronic energy intake of the three mealtimes, and immediate consumption of refined carbohydrates.

254

255 **4.1. How refined carbohydrates could affect cognition ?**

256 It has been suggested that carbohydrate-rich diet-related alterations in metabolic processes may cause
257 neurological injury prior to overt obesity or metabolic disease development, and that early-life exposure to refined
258 carbohydrates may be particularly toxic to cognitive functioning (for a review, see Hawkins et al., 2018). This
259 phenomenon could explain the relationship between the between-meal snack GL and the cognitive performance
260 observed in our study with healthy adult participants. The decrease in cognitive performance observed could be a first
261 biological consequence of chronic hyperinsulinemia and insulin resistance. Indeed, as mentioned earlier, between-
262 meal snack is a meal with high GL foods (Table 1), and the greater the GL is, the greater the spike of glycemia and

263 insulinemia. Thus, chronic exposure to a high-GL diet, such as between-meal snacks, could promote chronic
264 hyperinsulinemia and insulin resistance (Cao et al., 2007; Ludwig & Ebbeling, 2018; Mckeown et al., 2004).

265 The disturbance of brain cognitive functions by chronic hyperinsulinemia and insulin resistance could be due
266 to an alteration of brain glucose metabolism and of blood brain barrier permeability, and to a generation of oxidative
267 stress and inflammation (Arnold et al., 2018; Butterfield et al., 2014; Ma et al., 2015; Monnier et al., 2006). Cerebral
268 glucose hypometabolism has been identified in prediabetic and diabetic elderly individuals compared to nondiabetic
269 subjects (Baker et al., 2011), which can be explained either by a partial deregulation of insulin signaling decreasing
270 glucose entry into cells produced by chronic peripheral hyperinsulinemia (Benomar et al., 2006) or by insulin
271 resistance at the level of the blood brain barrier leading to a decrease in brain insulin concentration and insulin-
272 mediated brain cell activity (Arnold et al., 2018). In both hypotheses, the absorption and use of glucose by brain cells
273 is altered. In parallel, insulin resistance leads to mitochondrial dysfunction that promotes the formation of free
274 radicals, which produce excess oxidative stress (Butterfield et al., 2014). The damage caused by free radicals is
275 pivotal, as insulin resistance impairs the antioxidant defense capacities of cells (Kolb et al., 2020). Chronic
276 hyperglycemia can also alter proteins through a process of glycation, leading to the formation of a diverse group of
277 modified proteins known as AGEs (Advanced Glycation End products), which are able to attack other molecules
278 (Butterfield et al., 2014). In diabetic individuals, it is suggested that acute blood glucose fluctuations over daily period
279 exhibited a more specific triggering effect on oxidative stress than sustained chronic hyperglycemia estimated by
280 hemoglobin A1c (Monnier et al., 2006). Finally, insulin resistance could promote inflammation. It has been shown
281 that a high GL diet was associated with a higher concentration of CRP (C-reactive protein), a marker of systemic
282 inflammation (Liu et al., 2002), and that chronic hyperglycemia, induced by a high GL diet, led to an increase in the
283 plasma concentration of free fatty acids, which, in turn, stimulated the secretion of proinflammatory cytokines
284 (Butterfield et al., 2014; Litwiniuk et al., 2021).

285 Poor vascularization of the brain due to degradation of the capillary network by chronic hyperglycemia has
286 also been proposed to explain the disruption of brain cognitive function in relation to refined carbohydrate
287 consumption (Shigaeff et al., 2012).

288

289 **4.2. Why do the three chronic meals affect cognition differently?**

290 A relationship between refined carbohydrate content and cognitive performance was observed from only one
291 (between-meal snack) of the three meals examined. This meal is not the one with the higher mean GL and is not
292 particularly notable for its macronutrient content, carbohydrates, proteins, fats or fibers (Table 2). A possible
293 explanation is that these three types of meals could correspond to different ecological food habits that affect subjects
294 differently with different physiological consequences. Between-meal snacks, relative to the other meals, are often not
295 associated with physiological hunger and are mainly motivated by social or other external stimuli, with few resulting
296 effects on satiety and compensation mechanisms (Bellisle, 2014). Therefore, this meal category could better reflect
297 chronic and acute refined carbohydrate consumption. Interestingly, chronic energy intake during the afternoon snack
298 and breakfast also decreased cognitive performance. In the model, the effect of energy intake of each meal was
299 estimated at equal residual glycemic load and thus represented mainly the effects of fat and protein intake. One
300 possibility is that a large proportion of saturated fat is involved in these two meals, such as those found in pastries or
301 dairy; Fat is known to be an antagonist of insulin and a contributor to hyperinsulinemia and insulin resistance
302 (Kennedy et al., 2009), thus mimicking the potential negative effects of refined carbohydrates.

303

304 ***4.3. How the other control variables could affect cognition?***

305 We controlled for several other variables potentially affecting cognition in our study, such as BMI and
306 immediate intake of refined carbohydrates.

307 BMI was significantly associated with a decrease in cognitive performance in both sexes, although this effect
308 may be driven mainly by men (Table 5). The link between BMI and cognition is well established (Craft, 2007; Kim &
309 Feldman, 2015). Studies on obese people show that a high BMI is associated with a smaller brain, which negatively
310 affects cognition (Raji et al., 2010). Other studies have demonstrated an increased risk of cognitive dysfunction or
311 dementia in obese individuals even after adjustment for metabolic and vascular factors such as hypertension,
312 hyperlipidemia, metabolic syndrome, insulin resistance and diabetes (Rosengren et al., 2005; R. Whitmer et al., 2007;
313 R. A. Whitmer et al., 2005). The mechanisms involved have not yet been elucidated, but impaired vascularization of
314 the brain has been proposed to explain this phenomenon (Shigaeff et al., 2012). The lower impact of BMI on women's
315 cognition has already been discussed (Karlsson et al., 2021), and there is evidence that being overweight may
316 contribute to negative health outcomes differently in men and women (Bohn et al., 2020; Gannon et al., 2019). One

317 explanation could reside in the difference in body fat distribution between men and women, which is of importance, as
318 the location and type of fat stored affect the association between overweight and negative health outcomes (Sulc et al.,
319 2020).

320 The immediate intake of refined carbohydrates with a high or low glycemic breakfast influenced blood sugar
321 levels but had no impact on cognitive performance, whereas in the literature, an association between a low-GL
322 breakfast and better cognitive performance is generally reported (for a review see Edefonti et al., 2017). There are
323 several explanations for this result. First, it is possible that Wechsler's digit symbol substitution test is sensitive to
324 hypoglycemia: the brain is not supplied with optimal energy at a time when it is particularly in demand (Gold, 1995).
325 The duration of our experiment (1hour and 30 minutes after the end of breakfast) may have not allowed the cognitive
326 test to be performed during the period of hypoglycemia expected for high-GL breakfast B2 at $t = 1h30 - 2h$
327 (consecutive to an acute insulin response to B2-induced hyperglycemia). Second, the lack of effect may be related to
328 the fact that postprandial blood glucose levels affect the cognitive performances of young adults less, as found by
329 Sanchez-Aguadero et al., 2018 on several cognitive domains, such as attention, and executive functions also evaluated
330 by the Weschler cognitive test.

331

332 ***4.4. How can the influence of diet on health and cognition be evolutionary triggered?***

333 The adaptive landscape of the past human environments selected for multiple genetic, behavioral and
334 physiological traits. The transition to the industrial era rapidly reshaped these environments, resulting in evolutionary
335 mismatch, defined here as the phenomenon by which previously adaptive traits become maladaptive in a new
336 environment. The current mismatch between the way human physiology has evolved and Western industrialized
337 lifestyles has been proposed to explain the current epidemic of numerous diseases. Generally, traditional food (i.e.,
338 preindustrial or nonrefined) does not generate hyperglycemia or insulin resistance. This is the case for fresh fruits,
339 vegetables, legumes and traditionally prepared cereals. Traditional foods with a high level of sugar contents are
340 energetically rewarding, but they are typically seasonal or scarce, such as ripened fruit and honey. In the current
341 industrial dietary environment, foods that generate hyperglycemia, hyperinsulinemia and ultimately insulin resistance,
342 such as refined carbohydrates, are not quantitatively limited. In addition, humans did not evolve in such a dietary

343 environment. It is thus not surprising that this massive consumption of refined carbohydrates generates deregulation of
344 the insulin response system (Gunn-Moore et al., 2018), which now affects many aspects of health and well-being.

345

346 **4.5. Limitations**

347 Our study presents some limitations. First, the chronic effect of refined carbohydrate consumption on
348 cognitive performance observed here could be confounded by several variables not considered in this work. The main
349 and more complex meals (i.e., lunch and dinner), were not included, precluding the computation of an overall diet
350 quality index, which could have captured other aspects of diet influencing cognition (e.g., high fruit and vegetable
351 consumption, polyunsaturated fats). However, diet quality indices are correlated with low glycemic load food (higher
352 values for an increase in low glycemic load food; Azadbakht et al., 2016; Jones et al., 2016). Thus, diet quality
353 consumption was partially described by glycemic load measures. Second, even if the effect of diet on brain health is
354 well documented (Firth et al., 2020; Bremner et al., 2020), the converse is also possible as mental health, for example
355 the development of psychiatric disorders, can lead to changes in eating habits (Bremner et al., 2020). Thus direction of
356 causal effect are not straightforwardly determined. Third, the sample size of participants was relatively small, in
357 particular that of consumers of between-meal snacks (N = 24, Table 2), with the possibility that outliers have a
358 determinant influence. However, removing an outlier did not change qualitatively the results for RGL3. In addition,
359 repeatedly (1000 times) randomly removing 10 % of the total dataset, or 12.5 % (N = 3) of the pool of between-meal
360 snacks consumers, led to 94 % or 78 %, respectively, significant *P*-values (< 0.05) for the RGL3 variable, suggesting
361 that the effect detected is strong enough to be detected in a smaller sample size. Nevertheless, a small sample size
362 remains here a limitation of type 1 error. Fourth, concerning the method used to measure blood glucose for the
363 assessment of the effect of breakfast type on glycemia: although the glucose meter was conform to the ISO
364 15197:2013 norm, a direct measurement of blood glucose would have been more relevant leading to more accurate
365 results. Finally, we used a single cognitive test to assess cognitive performance. Even if the Wechsler's digit symbol
366 substitution covers many different cognitive domains (visual-motor coordination, mental and motor speed, executive
367 functions and attention; Hugonot-Diener et al., 2008), the use of other tests would have contributed additional
368 dimensions of cognition, for example, verbal episodic memory, immediate visual memory or global cognitive
369 function, currently used for the assessment of cognitive health and the diagnosis of neurodegeneration.

370

371 **4.6. Conclusion**

372 The recent Western dietary change, characterized mainly by the massive increase in refined carbohydrate
373 consumption, has well-known detrimental health consequences. Given the increasing number of people affected by
374 these pathologies and the repeated failure of many medical treatments, our study reinforces the belief that the most
375 promising research should focus on prevention in healthy persons. Indeed, we have shown that cognition in healthy
376 individuals is impacted by chronic refined carbohydrate consumption, indicating that neurocognitive deficits induced
377 by this type of diet may manifest before overt obesity, metabolic disease onset or dementia. Thus, the identification of
378 modifiable factors that could be targeted in interventions to prevent future health impairment is pivotal. Further
379 studies are needed to investigate what other potential health-related traits might be affected by refined carbohydrate
380 consumption in healthy people.

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383 **Competing interests statement**

384 The author(s) have declared no potential competing interests with respect to the research, authorship, and/or
385 publication of this article.

386

387 **Data Availability**

388 The data and R script associated with this research are available on Zenodo repository
389 [10.5281/zenodo.7031099](https://doi.org/10.5281/zenodo.7031099).

390

391 **Appendix A. Supplementary data**

392 Supplemental data for this article can be found online.

393

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417 **Table 1.** Number of individuals consuming the different food groups for each meal. N indicates the number of
418 consumers.

Food group	Women (N = 48)			Men (N = 47)		
	Breakfast (N = 48, 100%)	Afternoon snack (N = 26, 54%)	Between-meal snack (N = 12, 25%)	Breakfast (N = 47, 100%)	Afternoon snack (N = 19, 40%)	Between-meal snack (N = 12, 25%)
Cereals and bread	36	9	2	38	7	3
Biscuits, cakes, and pastries	9	11	4	8	11	3
Sweets and chocolate	20	13	5	29	8	9
Sweetened beverages	17	5	0	15	4	3
Dairy products	31	6	3	24	8	3
Fruits	16	13	3	13	6	4
Nuts	5	5	2	2	0	0

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425 **Table 2.** Descriptive statistics of food consumption for the three meals. Means and standard deviations (SDs) are
 426 given for consumers only. GL1, GL2 and GL3 are the three variables representing chronic refined carbohydrate
 427 consumption.

	Women (N = 48)			Men (N= 47)		
	Range	Mean	SD	Range	Mean	SD
Breakfast						
GL1	0-92	30.4	21.8	1-143	45.3	30.5
EI1	4-1038	377.3	245.1	8-1451	495.3	310.4
Carbohydrates (g)	0-144	42.8 (67%)	32.2	1-224	62 (70%)	41.4
Fat (g)	0-39	9.5 (17%)	9.4	0-55	13.4 (14%)	12.4
Protein (g)	0-27	6.7 (11%)	5.7	0-36	9.1 (10%)	7.7
Fiber (g)	0-17	3.7 (5%)	3.5	0-22	4.9 (5%)	4.1
Afternoon Snack						
GL2	0-62	13.1	16.7	0-128	16.4	29.4
EI2	0-985	184.9	244.6	0-1065	177.2	295.4
Carbohydrates (g)	0-103	19.6 (65%)	26.4	0-126	17.9 (74%)	30.9
Fat (g)	0-72	7.7 (19%)	13.6	0-42	3.5 (14%)	7.4
Protein (g)	0-23	3.2 (8%)	5.0	0-30	2.5 (8%)	5.8
Fiber (g)	0-16	2.3 (7%)	3.4	0- 10	1.3 (4%)	2.6
Between-Meal Snack						
GL3	0-42	3.8	9.2	0-110	7.5	19.4
EI3	0-622	63.6	149.0	0-1010	85.1	201.1
Carbohydrates (g)	0-66	4.7 (60%)	11.5	0-111	8.7 (71%)	21.4
Fat (g)	0-39	2.3 (24%)	6.7	0-23	1.9 (16%)	5.4
Protein (g)	0-19	1.1 (11%)	3.3	0-22	1.1 (7%)	3.6
Fiber (g)	0-8	0.6 (5%)	1.7	0-7	0.7 (6%)	1.7

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430 **Table 3.** Effects of breakfast type on the subject's glycemia of the participants. The type of breakfast, mean glycemia
431 for each, Wilcoxon test statistic (*W*) and corresponding *P*-value are given. Bold characters indicate significant (*P* <
432 0.05) effects. B1 was composed of nonrefined carbohydrates, and B2 was composed of refined carbohydrates.

Glycemia	Type of Breakfast	Mean glycemia (mg.dL ⁻¹)	<i>W</i>	<i>P</i>
G1 (before breakfast)	B1	85.8	1186	0.66
	B2	85.8		
G2 (30 minutes after breakfast)	B1	117.5	1846	< 10⁻⁷
	B2	144.3		
G3 (90 minutes after breakfast)	B1	94.5	1401	0.04
	B2	99.9		

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436 **Table 4.** Descriptive statistics of the subjects' physical characteristics

	Women (N = 48)			Men (N= 47)		
	Range	Mean	SD	Range	Mean	SD
Age (years)	20.0-28.1	22.7	2.1	20.0-29.8	23.1	2.1
BMI (kg/m ²)	16.4-28.8	21.7	2.6	16.5-37.4	23.3	3.9

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440 **Table 5.** Effects of different variables studied on Wechsler’s digit symbol substitution cognitive test performances.
 441 RGL1, RGL2 and RGL3 represent chronic refined carbohydrate consumption during breakfast, afternoon snack and
 442 between-meal, respectively. E1, E2 and E3 refer to energy intake during breakfast, afternoon snack and between-meal,
 443 respectively. For categorical data, the estimates are given for one category compared to the reference category
 444 (underlined term). The estimate (β), standard error of the mean (se), χ^2 statistic, and corresponding P -value are given.
 445 Bold characters indicate significant ($P < 0.05$) effects.

	β	se	χ^2	$P(>\chi^2)$
Intercept	62.049	1.866		
t	6.347	0.598	112.6	< 10^{-15}
t ²	-3.975	0.591	45.25	< 10^{-10}
RGL1	0.267	0.642	0.173	0.677
RGL2	0.535	0.675	0.627	0.428
RGL3	-1.639	0.706	5.389	0.020
EI1	-1.150	0.658	3.057	0.080
EI2	-1.457	0.712	4.183	0.040
EI3	0.736	0.656	1.256	0.262
Breakfast type (B1/ <u>B2</u>)	0.561	1.309	0.184	0.668
Age	-0.668	0.642	1.081	0.298
BMI	-3.042	0.892	8.432	0.003
Physical activity	0.364	0.687	0.281	0.596
Parental homeownership (yes/ <u>no</u>)	-0.372	1.810	0.042	0.837
Sex (Women/ <u>Men</u>)	1.657	1.364	0.918	0.338
BMI.sex (women with BMI/ <u>men with BMI</u>)	2.750	1.532	3.222	0.073

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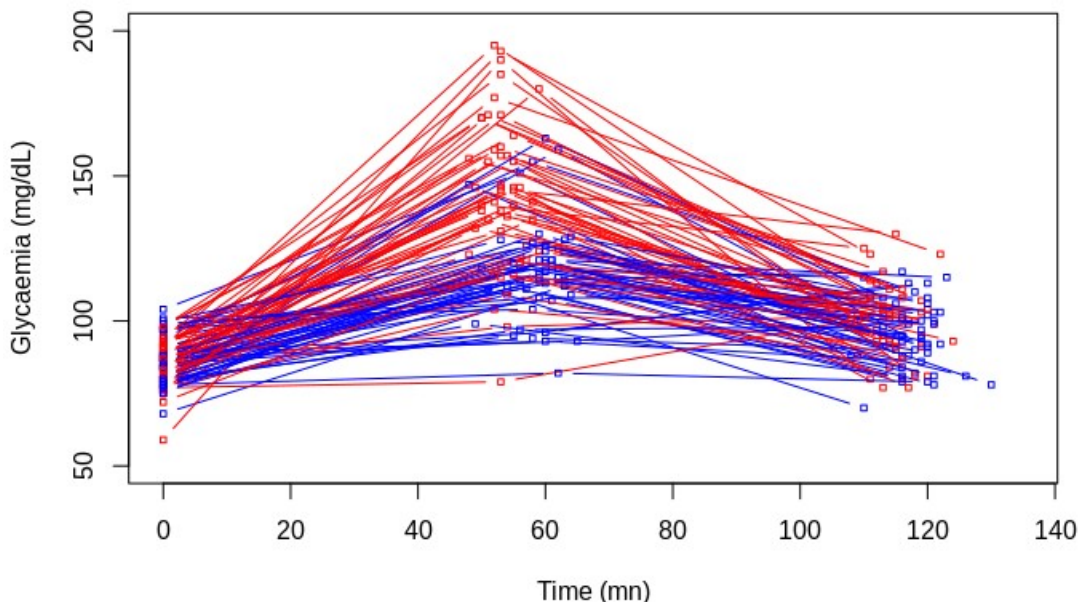
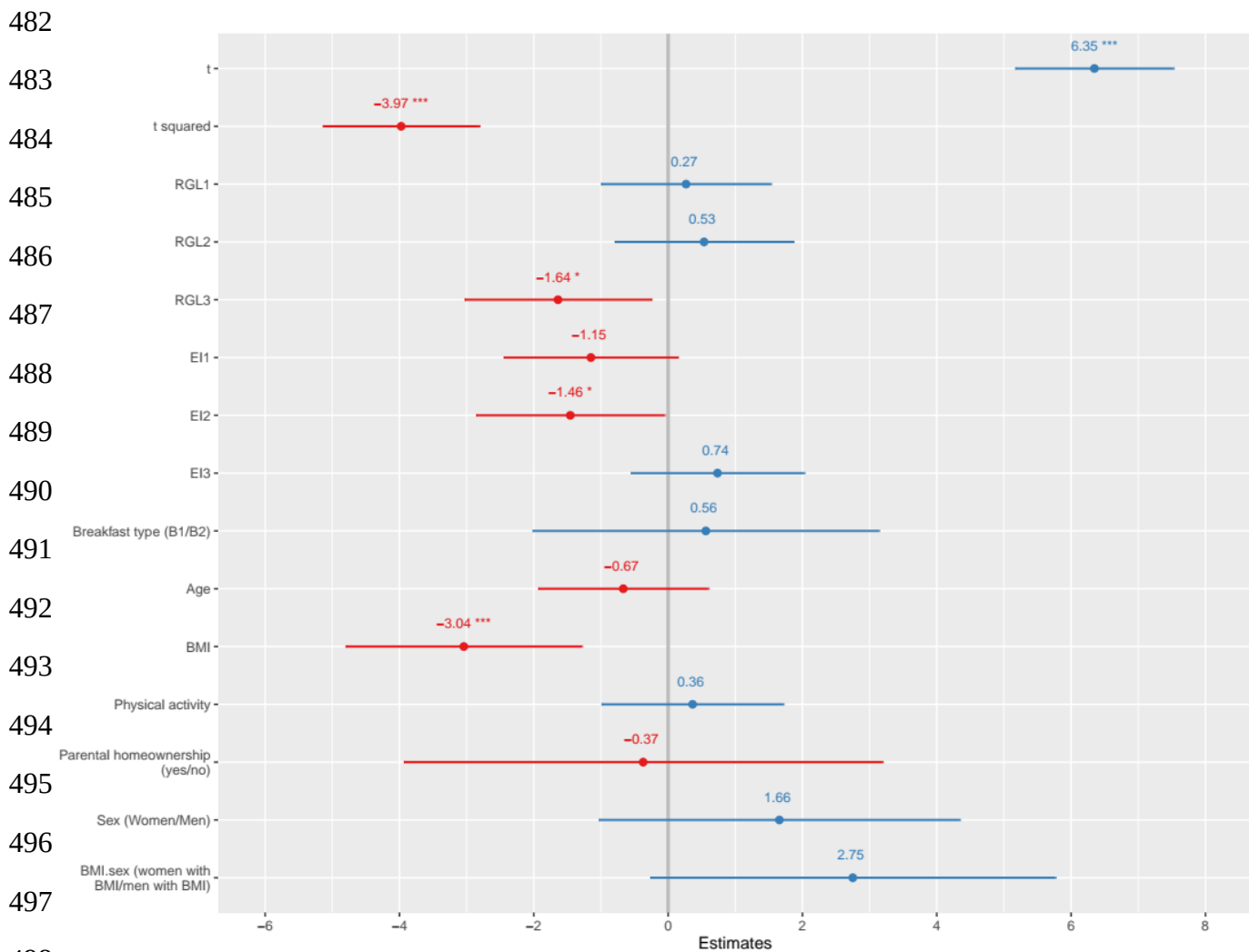


Figure 1. Effects of immediate breakfast consumption on glycemia. Glycemia from the low (B1) and high (B2) glycemic load breakfasts are represented in blue and red, respectively.



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500 **Figure 2.** Forest plot of the model of the impact of RGL1, RGL2 and RGL3 and control variables on the performance
 501 on Wechsler’s digit symbol substitution cognitive test. For categorical data, the estimates are for one category
 502 compared to the reference category (underlined term). * $P < 0.05$ ** $P < 0.01$ *** $P < 0.001$

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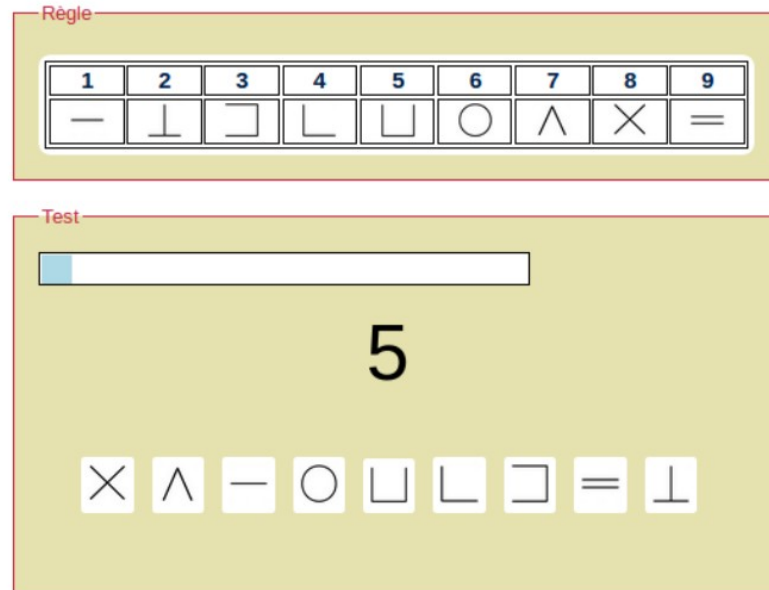
509 **Supplementary**

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523 **Figure S1.** Example from the
524 Wechsler’s digit symbol substitution cognitive test. The participant had to click on the correct symbol corresponding
525 to the displayed digit, according to the association rule above (Règle). Upon a choice, another randomly chosen digit
526 is proposed, with a shuffled list of symbols (but with the same association rule). The goal was to correctly associate as
527 many digits as possible with their corresponding symbol during the allocated time (blue bar).

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534 **Table S1.** Exhaustive list of the different food items of the diet questionnaire in French and translated.

French	English
Baguette (morceaux)	Baguette (pieces)
Pain (morceaux)	Bread (pieces)
Pain de campagne	Country bread
Pain complet	Whole wheat bread
Pain de mie	Soft bread
Pain de seigle	Rye bread
Pain poilane	Poilane bread
Pain découpé (restaurant-cantine)	Sliced bread (restaurant-canteen)
Couleur café au lait	Latte coffee color
Couleur chocolat au lait	Milk chocolate color
Blé soufflé	Puffed wheat
Müesli	Muesli
Pétales de maïs	Corn petals
Biscottes diverses	Various rusks
Brioche tranches ou individuelles	Sliced or individual brioche
Beurre	Butter
Epaisseur du beurre	Butter thickness
Confiture (consommation totale y compris tartine, boisson, laitage)	Jam (total consumption including toast, drink, dairy)
Miel (consommation totale y compris tartine, boisson, laitage)	Honey (total consumption including toast, drink, dairy)
Nutella (consommation totale y compris tartine, boisson, laitage)	Nutella (total consumption including toast, drink, dairy)
Sucre morceaux (consommation totale y compris boisson, laitage)	Sugar cubes (total consumption including drink, dairy)
Sucre poudre (consommation totale y compris boisson, laitage)	Granulated sugar (total consumption including drink, dairy)
Chèvre crottin	Goat cheese
Bûche	Goat cheese
Pyramide	Goat cheese
Boursin	Boursin
Camembert	Camembert
Rouy	Rouy
Gruyère	Gruyere
Mimolette	Mimolette
Roquefort	Roquefort
Tomme	Cheese
Fromage blanc	White cheese
Nombre de yaourts déjà sucrés à l'achat (aromatisé, aux fruits)	Number of yogurts already sweetened (flavored, with fruits)
Nombre de yaourts naturels	Number of plain yogurts
Nombre de petits-suisses nature	Number of plain Petits-Suisses
Yaourt à boire: nombre de verres	Drinkable yogurt: number of glasses
Taille du verre pour le yaourt à boire	Glass size for yogurt drink
Chantilly	Sweet whipped cream
Entremet semoule et riz	Semolina and rice dessert
Flan	Blank
Mousse au chocolat	Chocolate mousse
Gâteau à la crème	Cream cake
Gâteau mousse aux fruits	Fruit mousse cake
Tarte aux fruits	Fruit tart
Gâteau au chocolat	Chocolate cake
Tourte aux amandes	Almond pie
Cake	Cake
Madeleines	Madeleines
Quatre-quarts	Pound cake

Type de biscuits consommés	Type of cookies eaten
Nombre de biscuits consommés	Number of cookies eaten
Nombre de viennoiseries consommées (croissant, pain au chocolat, ...)	Number of pastries consumed (croissant, pain au chocolat, etc.)
Noix	Nut
Noisettes	Hazelnut
Pistaches	Pistachios
Cerises	Cherries
Fraises	Strawberries
Framboises	Raspberries
Banane	Banana
Pomme	Apple
Poire	Pear
Kiwi	Kiwi
Abricot	Apricot
Groseilles	Currants
Quetsches (prunes)	Quetsches (plums)
Raisins	Grapes
Orange	Orange
Pruneaux	Prunes
Ananas au sirop	Pineapple in syrup
Fruits au sirops divers	Fruits in various syrups
Bonbons divers	Various candies
Chocolat (carrés)	Chocolate (squares)
Barre chocolatée	Chocolate bar
Soda, jus de fruit: nombre de boissons individuelles consommées (canette-bouteille-brick)	Soda, fruit juice: number of individual drinks consumed (can-bottle-brick)
Type de contenant de boisson individuelle (canette-bouteille-brick)	Type of individual beverage container (can-bottle-brick)
Soda, jus de fruit: nombre de verres	Soda, fruit juice: number of glasses
Taille du verre (soda ou jus)	Glass size (soda or juice)
Taille de la tasse ou du bol (lait-café-chocolat)	Cup or bowl size (milk-coffee-chocolate)