

Title page

Relationship between sensory liking for fat, sweet or salt and cardiometabolic diseases; mediating effects of diet and weight status

Aurélie Lampuré¹ a.lampure@eren.smbh.univ-paris13.fr, Solia Adriouch¹ s.adriouch@eren.smbh.univ-paris13.fr, Katia Castetbon² katia.castetbon@ulb.ac.be, Amélie Deglaire³ amelie.deglaire@agrocampus-ouest.fr, Pascal Schlich⁴ pascal.schlich@dijon.inra.fr, Sandrine Péneau¹ s.peneau@eren.smbh.univ-paris13.fr, Léopold Fezeu¹ l.fezeu@eren.smbh.univ-paris13.fr, Serge Hercberg^{1,5} s.hercberg@eren.smbh.univ-paris13.fr, Caroline Méjean^{1,6} caroline.mejean@inra.fr

¹ Université Paris 13, Equipe de Recherche en Epidémiologie Nutritionnelle, Centre de Recherche en Epidémiologie et Statistiques, Inserm (U1153), Inra (U1125), Cnam, COMUE Sorbonne Paris Cité, F-93017, Bobigny, France.

² Université Libre de Bruxelles, Ecole de Santé Publique, Centre de Recherche en Epidémiologie, Biostatistiques et Recherche Clinique, B-1070 Bruxelles, Belgique.

³ Inra, UMR 1253, Science et Technologie du Lait et de l'Œuf, Rennes, France.

⁴ Centre des Sciences du Goût et de l'Alimentation, UMR 6265 CNRS, UMR 1324 Inra, Dijon, France.

⁵ Département de Santé Publique, Hôpital Avicenne (AP-HP), Bobigny, F-93017, France.

⁶ INRA, UMR 1110 MOISA, F-34000 Montpellier, France.

Corresponding author: Aurélie Lampuré

EREN, SMBH Paris 13, 74 rue Marcel Cachin, F-93017 Bobigny Cedex, France

Phone number: 00 33 1 48 38 89 44 / Fax number: 00 33 1 48 38 89 31

E-mail: a.lampure@eren.smbh.univ-paris13.fr

Conflicts of interests

The authors declare that they have no conflicts of interest.

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1 **Abstract**

2 Purpose: It has been suggested that individual sensory liking is an important
3 predictor of dietary intake and weight status, and may consequently influence
4 development of cardiometabolic diseases (CMDs). We investigated the association
5 between sensory liking for fat-and-salt, fat-and-sweet, sweet or salt and the onset of
6 hypertension, diabetes and cardiovascular diseases (CVDs) over 6 years in adults,
7 and the mediating effects of dietary intake and BMI.

8 Methods: We examined the CMDs risk among 41,332 (for CVD and diabetes) and
9 37,936 (for hypertension) French adults (NutriNet-Santé cohort). Liking scores,
10 individual characteristics, diet and anthropometry were assessed at baseline using
11 questionnaires. Health events were collected during 6 years. Associations between
12 sensory liking and CMDs risk, and the mediating effect of diet and BMI, were
13 assessed using Cox proportional hazards models.

14 Results: Sensory liking for fat-and-salt was associated with an increased risk of
15 diabetes, hypertension and CVD (hazard ratios (HR) for 1-point increment of the
16 sensory score: HR=1.30 [95%CI 1.18,1.43], HR=1.08 [1.04,1.13] and HR=1.10
17 [1.02,1.19], respectively). BMI and dietary intake both explained 93%, 98% and 70%,
18 of the overall variation of liking for fat-and-salt liking in diabetes, hypertension and
19 CVD, respectively. Liking for fat-and-sweet and liking for salt were also associated
20 with an increased risk of diabetes (HR=1.09 [1.01,1.17] and HR=1.09 [1.01,1.18],
21 respectively) whereas liking for sweet was associated with a decreased risk
22 (HR=0.76 [0.69,0.84]).

23 Conclusions: Higher liking for fat-and-salt is significantly associated with CMDs risk,
24 largely explained by dietary intake and BMI. Our findings may help to guide effective
25 targeted measures in prevention.

26 **Keywords**

27 Cardiovascular disease, diabetes, hypertension, sensory liking, dietary intake,
28 mediating factor

29 **Background**

30 Cardiovascular disease (CVD) is the cause of death of 18 million people around the
31 world, with diabetes and hypertension as the major risk factors [1]. The role of
32 excessive consumption of saturated and trans fats, simple sugar and sodium in the
33 etiology of major chronic diseases and increased mortality has been well
34 documented in literature [2-4]. Most public health programs worldwide target
35 nutritional recommendations, which include limitations in fat, salt and sugar intake
36 [2,5]. However, these components contribute to eating pleasure due to the sensory
37 properties they drive, and the important effect of sensory function on food intake has
38 been highlighted [6]. Individual sensory liking for fat appears to be a potential
39 determinant of dietary intake [7-9] and weight status [10-12], and may consequently
40 influence development of CMDs (defining as hypertension, diabetes and CVD in our
41 study). In addition, the specific role of sweet and salt liking in food intake need further
42 research, especially in a large cohort.

43 To our knowledge, very few studies have investigated relationships between sensory
44 liking and CMDs. A cross-sectional study with a convenience sample of 88 women
45 has shown that women reporting higher liking for high-fat foods had greater adiposity
46 and blood pressure [13]. Another cross-sectional study has highlighted that fat
47 preference was associated with higher BMI and waist circumference in men, and no
48 association was found with sweet preference [14]. Furthermore, a case-control study
49 has shown that heart failure patients had higher salt liking than healthy volunteers. In
50 addition, salt preference was associated with increased mortality from stroke in men
51 and women in a Japanese cohort study [15]. In previous studies, sensory liking
52 components considered were limited, evidence is still lacking on this topic and
53 hypotheses need to be further investigated.

54 No study has investigated the contribution of dietary intake and body mass index
55 (BMI) to explain the influence of sensory liking on CMDs. Nevertheless, sensory fat
56 liking has already been highlighted as strongly associated with higher fat intake but
57 also with lower intake of nutrient-dense foods such as fruits and vegetables, dairy
58 products, whole grains products and fish [7-9], which increased the risk of weight
59 gain and obesity [10-12]. This emphasizes the need to consider the overall dietary
60 intake and body mass index as potential mediators in the relationship between high
61 liking for fat, sweet or salt and the CMDs risk.

62 The aim of our study was therefore to assess the prospective association between
63 individual liking for fat-and-salt, fat-and-sweet, sweet or salt and the risk of
64 developing CVDs, type 2 diabetes and hypertension over 6 years, in a large
65 population of French adults. In addition, we investigated the mediating effect of
66 dietary intake and weight status on the relationship between sensory liking and
67 CMDs.

68 **Methods**

69 Study population

70 We used data from the NutriNet-Santé study, a large web-based observational cohort
71 launched in France in 2009 with a scheduled follow-up of 10 years. It was
72 implemented in a general population and targeted Internet-using adult volunteers.
73 Briefly, eligible participants were recruited by a variety of means. Initially a vast
74 multimedia campaign called for volunteers, then campaigns were repeated every six
75 months. Further information is maintained on a large number of websites (national
76 institutions, city councils, private firms) and a billboard advertising campaign is
77 regularly updated via professional channels (e.g., doctors, pharmacists, dentists,
78 business partners, municipalities). The study was designed to investigate the
79 relationship between nutrition and health, as well as determinants of dietary behavior
80 and nutritional status [16]. Briefly, in order to be included in the cohort, participants
81 had to fill out an initial set of questionnaires assessing dietary intake, physical
82 activity, anthropometry, lifestyle, socio-economic conditions and health status. As
83 part of their follow-up, participants complete the same set of questionnaires every
84 year. Moreover, each month, they are invited to fill out complementary questionnaires
85 related to determinants of dietary behavior, nutritional and health status. All
86 questionnaires are completed online via the NutriNet-Santé website. Compared to
87 the general population, included individuals were more often women, relatively more
88 educated and those who are married were notably larger than the general French
89 population [17].

90 This study was conducted according to guidelines laid down in the Declaration of
91 Helsinki, and all procedures were approved by the Institutional Review Board of the

92 French Institute for Health and Medical Research (IRB Inserm
93 n°0000388FWA00005831) and the “Commission Nationale Informatique et Libertés”
94 (CNIL n°908450 and n°909216). Electronic informed consent was obtained from all
95 subjects. This study is registered in EudraCT (n°2013-000929-31).

96 Data collection

97 *Assessment of liking for fat-and salt, fat-and-sweet, sweet and salt*

98 Liking for fat-and-salt, fat-and-sweet, sweet and salt was assessed using PrefQuest,
99 an original web-based questionnaire [18]. In May 2010, included participants in the
100 Nutrinet-Santé cohort (n=65,683) were invited to complete this questionnaire
101 available online for six months. This questionnaire assesses liking for fat, saltiness
102 and sweetness via several items, enabling an assessment of overall liking, i.e. liking
103 primarily derived from sensation independently of the food product. The development
104 and validation of the questionnaire have been described elsewhere [18]. Briefly,
105 PrefQuest is composed by 83 items divided into liking for salt (11 items) and sweet
106 (21 items) tastes, fat-and-salt (31 items) and fat-and-sweet (20 items) sensations.
107 The questionnaire included four types of items: (i) liking for sweets, fatty-sweet and
108 fatty-salty foods; (ii) preferred level of salt, sweet, fat-and-salt or fat-and-sweet
109 seasoning; (iii) preferred drinks (sweet/sweetened or unsweetened) on a restaurant
110 menu; and (iv) dietary behavior in terms of sweet, salty and fatty foods. PrefQuest
111 was internally validated by studying the underlying structure of each taste using
112 exploratory factor analysis and confirmatory factor analysis, and also compared with
113 sensory tests that included 32 food models conducted in a diversified sample (n=557)
114 [19] (Deglaire et al. 2011, personal communication). The salty taste was
115 unidimensional, unlike the sweet taste and the fat sensation. The sweet taste was

116 formed by the factors 'sweet foods', 'added sugar' and 'natural sweetness' and the fat
117 sensation was composed of the fat-and-salt sensation based on 'added fat-and-salt'
118 and 'fatty-salty foods' and the fat-and-sweet sensation based on 'added fat-and-
119 sweet' and 'fatty-sweet foods'.

120 *Events' ascertainment*

121 Participants self-declared health events through the yearly health status
122 questionnaire (in which they can also declare family medical history), using a specific
123 check-up questionnaire for health events (every three months) or at any time through
124 a specific interface on the study website. Following this declaration, participants were
125 invited to send their medical records (diagnosis, hospitalization, radiological reports,
126 electrocardiograms, etc.). If necessary, the study's physicians contacted the
127 participants' treating physician or the medical structures to collect additional
128 information. Then, data were reviewed by an independent physician expert
129 committee, which validated all major health events. The present study focused on
130 cases of hypertension, type 2 diabetes, and cardiovascular events (strokes, transient
131 ischemic attacks, myocardial infarctions, acute coronary syndromes and
132 angioplasties) diagnosed between May 2010 and November 2016.

133 *Assessment of dietary intake*

134 At enrollment and each year thereafter, participants were invited to provide three
135 non-consecutive validated web-based 24h dietary records randomly assigned over a
136 2-week period (1 weekend day and 2 weekdays). The accuracy of web-based 24h
137 dietary records has been assessed by comparing to interviews by trained dietitians
138 [20] and against 24h urinary and blood biomarkers [21,22]. The dietary record was
139 completed via an interactive interface designed for self-administration on the Internet.

140 The web-based dietary assessment method relied on a meal-based approach,
141 recording all foods and beverages (type and quantity) consumed at breakfast, lunch,
142 dinner and all other eating occasions. Portion sizes were assessed via a validated
143 picture booklet [23] or according to standard measurements. Foods were classified
144 according to the information provided in the French National Nutrition and Health
145 Program guides [24]. Food groups (in grams/day) considered in the present study
146 were vegetables, fruits, meat, processed meat, fish, starchy foods, whole grain
147 products, milk and yogurt, cheese, butter and other added fats, oil, sugar and
148 sweetened products, sweetened cream desserts, fatty-sweet products, savory
149 sauces, salted snacks and appetizers, sweetened soft drinks and alcoholic
150 beverages. Values for energy were estimated using published nutrient databases
151 [25]. We used the three closest dietary records to the PrefQuest questionnaire (or
152 two if one was missing).

153 *Anthropometric data*

154 Height and weight data were collected at enrollment and each year thereafter by a
155 validated self-administered anthropometric questionnaire [26]. BMI (kg/m^2) was
156 calculated as the ratio of weight to the square of height. The closest available
157 anthropometric data to the PrefQuest questionnaire were used in this analysis.

158 *Sociodemographic and lifestyle data*

159 Potential confounding factors of the relationship between sensory liking for fat-and-
160 salt, fat-and-sweet, sweet or salt and the CMDs risk previously identified [27-29] were
161 collected using web-based questionnaires at the same time as sensory liking data:
162 age (years), sex, education (elementary school, secondary school, college graduate
163 or advanced degree), smoking status (never, former or current smoker), and physical

164 activity level using the short French version of the International Physical Activity
165 Questionnaire (low, moderate or high) [30].

166 Statistical analyses

167 The present analysis focused on participants of the NutriNet-Santé cohort, living in
168 metropolitan France, who had completed the PrefQuest and the set of
169 complementary questionnaires, and who had self-reported health information, even
170 no event to declare, over 6 years of follow-up.

171 Liking scores for fat-and-salt, fat-and-sweet, salt and sweet were computed as
172 detailed previously, ranging from 0 to 10 and considered as continuous variables
173 [18,27]. Regarding dietary intake, for each participant, daily mean quantities of the
174 food group (in grams) and energy intake were calculated from two or three 24h
175 records, weighted according to the day (week or weekend). Diet-underreporting
176 participants were identified by the method proposed by Black [31]. Briefly, basal
177 metabolic rate (BMR) was estimated by Schofield equations [32] according to sex,
178 age, weight and height collected at enrollment in the study. Energy intake and BMR
179 were compared to a physical activity level of 1.55 or below, the WHO value for 'light'
180 activity, to identify energy-underreporting subjects [31]. They were consequently
181 excluded for analysis.

182 Comparisons between included and excluded participants were performed using
183 Student's t-test and chi-square test, as appropriate. Individual characteristics and
184 dietary intake were compared between individuals who have developed a CMD
185 during the follow-up and those who had not, using Student's t-test and chi-square
186 test, as appropriate. Dietary intake and BMI were compared between quartiles of
187 liking for fat-and-salt, fat-and-sweet, salt and sweet using analysis of covariance. Sex

188 interaction has been tested but was not significant. Cox proportional hazard models
189 with age as the primary time variable were used to calculate hazard ratios (HR) and
190 95% confidence intervals (95% CI) for 1-point increment of the sensory score, for the
191 association between scores of sensory liking for fat-and-salt, fat-and-sweet, sweet
192 and salt and the risk of cardiometabolic diseases. First, Cox base models were
193 performed to study the effect of liking for fat-and-salt, fat-and-sweet, sweet and salt
194 on the risk of developing cardiovascular diseases (CVD), type 2 diabetes or
195 hypertension, adjusted for sex. Secondly, education, smoking status, alcohol
196 consumption, physical activity and family medical history (CVD, diabetes and
197 hypertension) were added in the h model as confounding factors. Thirdly, to assess
198 the mediating effect of dietary intake, we selected food groups which were
199 associated with CVD, type 2 diabetes or hypertension risk, as well as with liking for
200 fat-and-salt, fat-and-sweet, sweet or salt using Cox and linear regression models, as
201 appropriate ($P \leq 0.10$). Then, Cox models assessing the mediating effect of dietary
202 intake on the relationship between sensory liking and the risk of cardiometabolic
203 diseases were performed adjusted for daily energy intake and month of inclusion.
204 Finally, BMI was added to the previous model to assess its mediating effect on the
205 relationship between sensory liking and risk of cardiometabolic diseases.

206 The magnitude of the mediating effect was assessed by the percentage change in
207 the HRs between models computed as $[(HR \text{ base model} - HR \text{ base model} +$
208 $mediator) / (HR \text{ base model} - 1)] \times 100$ [33]. Dietary intake and BMI were considered
209 as a mediating factor when the percentage change of the HR was higher than 10%
210 and there was no increase of other HRs [33]. In addition, we calculated the part of
211 the reduction in deviance attributable to sensory liking, which was accounted for by
212 inclusion of the potential mediator and confounders. The reduction in deviance

213 related to sensory liking quantifies the percentage of the sensory liking impact on the
214 outcome explained by the mediator/confounder [34]. The deviance of sensory liking
215 in the base model was compared to the deviance of sensory liking in the extended
216 model. The percentage of reduction of deviance (RD) due to sensory liking explained
217 by inclusion of the mediating factor or confounders was calculated as follows [(RD
218 due to sensory liking in base model) – (RD due to sensory liking in base model +
219 mediator/confounders) / RD due to sensory liking in base model] × 100 [33].

220 The actuarial method was used and assumptions of proportionality were satisfied
221 through examination of the log-log (survival) compared with log-time plots. Data
222 management and statistical analyses were performed using SAS software (version
223 9.3, SAS Institute Inc, Cary, NC, USA). Criteria for statistical significance was
224 $p < 0.05$ and for practical significance was $> 10\%$ change of HRs.

225 **Results**

226 Among the 65,683 participants in the NutriNet-Santé study in May 2010, 49,066
227 responded to the PrefQuest (75% participation rate). Among responders, 48,336 had
228 available health information in 2010. Then, we excluded 1902 subjects with a history
229 of CVD or with diabetes at baseline, 3785 who were identified as diet-underreporting
230 participants or who did not answer to 24h dietary records in 2010 and 1327 women
231 who were pregnant at baseline, which left 41,322 participants available for analysis of
232 cardiovascular diseases and diabetes (32,055 women and 9267 men). Regarding
233 hypertension analysis, starting from the 48,336 participants, 5609 subjects with a
234 history of CVD or hypertension at baseline were excluded, as well as 3469 who did
235 not have dietary intake data and 1322 pregnant women, which left 37,936
236 participants for analysis of hypertension (29,828 women and 8108 men). Compared
237 with excluded subjects, individuals included in our analysis were slightly younger,
238 had a lower BMI, the percentage of those with high education was higher and the
239 proportions of men and smokers were lower ($P<0.05$; data not shown).

240 During a median follow-up of 5.5 y, 655 individuals developed CVD (342 women and
241 313 men), 342 developed type 2 diabetes (205 women and 137 men), and 1907
242 developed hypertension (1264 women and 643 men).

243 Sociodemographic characteristics, lifestyle and dietary intake according to
244 cardiometabolic status are presented in **Table 1**. Individuals with cardiometabolic
245 diseases were older, less often women, and had higher BMI than individuals who did
246 not developed a CMD during the follow-up. A smaller proportion had a university
247 degree, a higher proportion were former smokers, they were less physically active
248 (except for diabetes subjects), and had higher percentages of family medical history

249 than healthy individuals. Finally, subjects with CMD had higher intake of energy,
250 alcohol, fish and starchy foods, whereas they had lower intake of fatty-sweet
251 products compared with healthy individuals at baseline.

252 Food group consumption and BMI according to liking levels were presented in
253 supplementary tables S1 and S2. Individuals with higher liking for fat-and-salt, fat-
254 and-sweet, salt and sweet (quartile 4) had lower intake of fruits, vegetables and
255 whole grain products, but higher intake of meat, processed meat, cheese, butter and
256 other added fats, salted snacks and appetizers, savory sauces, starchy foods,
257 sweetened soft drinks and higher energy intake compared to individuals with lower
258 liking for fat-and-salt, fat-and-sweet, salt and sweet (quartile 1). In addition, higher
259 BMI was found in individuals with higher liking for fat (fat-and-salt and fat-and sweet)
260 and salt.

261 Hazard ratios for 1-point increment of the sensory score of associations between
262 sensory liking for fat-and-salt, fat-and-sweet, sweet and salt, and the risk of CMDs
263 are presented in **Tables 2, 3 and 4**. Liking for fat-and-sweet, sweet and salt were not
264 associated with CVD risk (HR=0.96 [0.91;1.02] p=0.15, HR=0.97 [0.90;1.04] p=0.37
265 and HR=0.98 [0.93;1.04] p=0.44, respectively) and with risk of hypertension
266 (HR=0.98 [0.95;1.02] p=0.34, HR=0.99 [0.95;1.04] p=0.79 and HR=0.99 [0.96;1.03]
267 p=0.63, respectively), results were therefore not tabulated.

268 In base model (table 2), liking for fat-and-salt was associated with increased risk of
269 cardiovascular diseases (increased risk of 10%), and when dietary intake was adding
270 to the model, the association became non-significant. Dietary factors explained 30%
271 of the decreased HRs in CVD (RHR), and the addition of BMI explained 40%. In
272 addition, dietary factors furthermore explained 61% (RD) of the overall variation of

273 fat-and-salt liking, i.e. sensory liking reduction in deviance in CVD, and dietary factors
274 and BMI explained together 70% of the overall variation of fat-and-salt liking in CVD.

275 Liking for fat-and-salt was associated with increased risk of developing type 2
276 diabetes (increased risk of 30%) whereas sweet liking was associated with lower risk
277 (24%) (table 3). Dietary intake and BMI largely explained together the decreased HR
278 for fat-and-salt liking (73%) and the increased HR for sweet liking (54%), and they
279 explained 93% and 84% of the overall variation of fat-and-salt and sweet liking in
280 diabetes, respectively. Furthermore, fat-and-sweet and salt liking were associated
281 with a higher risk of type 2 diabetes, but the practical criterion was not met (9%).

282 Finally, liking for fat-and-salt was associated with increased risk of developing
283 hypertension but the criteria for practical significance was not met (8%) (table 4). In
284 addition, with diet and BMI, the association became not statistically significant, and
285 they explained together 88% of the decreased HRs in hypertension. The overall
286 variation of fat-and-salt liking in hypertension was largely explained by dietary intake
287 and BMI (98%).

288 Discussion

289 This prospective study highlights original findings on the influence of sensory liking
290 on cardiometabolic disease risk. We have shown that liking for fat-and-salt was
291 prospectively associated with an increased risk of CVD, type 2 diabetes and
292 hypertension, and diet and BMI substantially explained this relationship. Results have
293 also raised that liking for fat-and-sweet and salt liking were statistically associated
294 with an increased risk of diabetes, mainly explained by dietary intake and weight
295 status. Sweet liking was associated with a decreased risk of diabetes, partially
296 explained by diet and BMI. Finally, no relationship was found between fat-and-sweet,
297 sweet and salt liking, and incidence of CVD and hypertension.

298 Findings regarding the positive association between fat-and-salt liking and the risk of
299 CMDs are concordant with previous cross-sectional studies that highlighted liking for
300 fat as a predictor of adiposity and blood pressure in women [13], and a positive
301 association with BMI and waist circumferences in men [14]. In these studies, only
302 liking for fat was assessed, but due to the higher numbers of fatty-salty foods items
303 compared to fatty-sweet items, fatty-salty foods had potentially more weight than
304 fatty-sweet foods in liking assessment. We have highlighted that dietary intake and
305 BMI substantially explained the relationship between fat-and-salt liking and the risk of
306 CVD, diabetes and hypertension. A previous study conducted in the NutriNet-Santé
307 cohort has shown that individuals with higher fat-and-salt liking were more likely to
308 have high intake of energy and fatty foods, compared to individuals with lower fat-
309 and-salt liking [7]. Excessive consumption of red meat, processed meat and
310 especially processed food rich in trans fat, is associated with higher risk of
311 cardiometabolic diseases [35-37]. Participants with high fat liking may be less
312 interested in healthy foods because they find them less tasty; consequently, they

313 may tend to replace healthy foods by their energy-dense variants [7]. In addition, the
314 large variation in fruit and vegetable intake according to levels of liking for fat-and-salt
315 may contribute to this increased risk, highlighted in a previous study [7] in
316 concordance with our data (supplementary table S1). Indeed, this difference [110 g/d
317 in women and 139 g/d in men] represents more than one serving per day, i.e. 80 g,
318 as defined by international recommendations [38]. Much research has shown
319 beneficial effects upon cardiometabolic morbidity of additional servings of fruits and
320 vegetables [39,40] that may greatly explained the effect of fat-and-salt liking on
321 CMDs.

322 Furthermore, in the same cohort, obese individuals had higher fat-and-salt liking
323 scores compared to normal-weight participants in a cross-sectional design [41] and
324 men with high fat-and-salt liking were more at risk to become obese over 5 years
325 [10]. High liking for fat-and-salt therefore appears to predict higher risk of developing
326 CMDs, mediated by unhealthy dietary intake and higher BMI. In addition, education,
327 lifestyle and family medical history also contribute to explain the association between
328 fat-and-sat liking and CVD. It has already been shown in NutriNet santé cohort study
329 that high liking for fat-and-salt was associated with low socioeconomic position and
330 smoking [27] which are risk factors of CVD. Indeed, the harmful effects of smoking
331 [42], low educational level [43] and physical inactivity [44] on CVD risk are well-
332 known, regardless of dietary intake and BMI effects.

333 Liking for fat-and-sweet sensation and liking for salty taste were statistically
334 significantly associated with an increased risk of type 2 diabetes and both
335 associations were mainly but partially explained by dietary intake and weight status.
336 Indeed, individuals with high liking for salt and fat-and-sweet had unhealthy dietary
337 intake which can contribute to explain the increased risk of diabetes [45]. Individuals

338 with high liking for fat-and-sweet, compared to those with low liking, had higher intake
339 of energy, sweetened soft drinks, fatty-sweet products, cream desserts and
340 processed meat, and lower intake of fruits, vegetables and whole grain products
341 (supplementary table S1). In addition, individuals with higher liking for salt had also
342 unhealthy food intake, compared with those who have a lower liking, with higher
343 intake of energy and alcoholic beverages and lower intake of whole grain products,
344 fruits and vegetables (supplementary table S2).

345 Regarding salt preference, we did not replicate results of the study of Ikehara et al.
346 [15] which have highlighted that high salt preference was associated with a 20%
347 increased risk of mortality from stroke. When we considered only stroke as events in
348 our study, the relationship was not significant [data not shown] and the fact that we
349 did not study the mortality. However, as in our study, they failed to show a
350 relationship between total CVD mortality and high salt preference [15]. Although salt
351 liking is predictive to sodium use, and sodium intake is associated with CVD
352 incidence [46], expected association was not found in our study, probably due to salt
353 liking assessment. Indeed, salt liking was mainly assessed by questions about
354 preferred level of salt seasoning, since salty foods without fats are not consumed in
355 the French food culture [18]. But as more than 75% of the daily sodium intake comes
356 from industrially processed foods which are also rich in fats [47], this may explain the
357 absence of association between liking for salt and CMDs.

358 Our results surprisingly showed that liking for sweet taste was associated with a
359 decreased risk of diabetes, and was not associated with CVD or hypertension risks.
360 In a previous work, we have shown that liking for sweet was also associated with a
361 decreased risk of obesity, driven by liking for natural sweetness, and mediated by
362 healthy dietary intake [10]. When analysing the association of sub-factors of sweet

363 liking with diabetes risk, i.e. sweet foods, natural sweetness and added sugar, the
364 inverse association was driven by liking for natural sweetness (i.e. honey, added jam,
365 sweet dried fruits) and liking for added sugar (i.e. sugar in coffee, yogurt, crepe).
366 Considering dietary intake of individuals with higher liking for natural sweetness, they
367 had a diet rich in fruits, vegetables and whole grain products, compared to those with
368 lower liking. Surprisingly, those with high liking for added sugar had food intake
369 similar to those with high liking for fat-and-sweet, but had slightly lower BMI
370 (supplementary tables S1 and S2), which can contribute to explain the difference of
371 results. In addition, as liking for fat-and-sweet is statistically associated with higher
372 risk of diabetes, this may suggest that the fatty component of fat-and-sweet liking is
373 driving the increased risk of diabetes.

374 Interpretation of the present results must take into account several limitations.
375 Subjects were volunteers in the NutriNet-Santé cohort so probably more concerned
376 about healthy lifestyle and nutrition than the general population. Moreover,
377 incidences of CVD, type 2 diabetes and hypertension in participants were lower than
378 in the general French population [48] which might underestimate our association.
379 Caution is therefore needed when interpreting and generalizing the results. In
380 addition, dietary data were collected using 24h dietary records, which can
381 underestimate energy intake [49]. Individual characteristics, sensory liking and
382 dietary intake were assessed at baseline only, so cumulative effect of these
383 behaviors on the development of CMDs could not be assessed. Furthermore,
384 residual confounding cannot be excluded because other confounders of sensory
385 liking in CMDs risk such as genetics or psychological factors could not be taken into
386 account in the analysis. Finally, some association did not succeed to attain the cut-off
387 of 10% for practical significance, thus low effect sizes of some HRs suggest caution

388 when interpreting. However, the strength of our study is its prospective design with
389 the 6 years of follow-up that allows us to explore the inference of causality between
390 sensory liking and the CMDs risk. Another limitation was that self-reported data could
391 be not accurate as measured data. Compared with liking as assessed by sensory
392 tests, self-reported liking by questionnaire may lead to misreporting. Recalled liking
393 can be influenced by the recalled pleasure arising from the sensory cues, but also by
394 other external cues such dietary habit, dietary restraint, social desirability, health
395 considerations and other variables [9,50]. However, this questionnaire was carefully
396 developed through a series of pretests and pilots that demonstrated its repeatability,
397 feasibility and internal validity [18], and positive correlations with sensory test
398 measurements have been shown (Deglaire et al. 2011 personal communication).
399 Although CMDs were validated, misclassification bias has to be considered as they
400 were also self-reported.

401 **Conclusions**

402 In conclusion, fat-and-salt liking was associated with an increased risk of
403 hypertension, diabetes and CVDs, mainly explained by unhealthy dietary intake and
404 BMI. Our findings have clinical implications for management of persons at risk of
405 chronic diseases. Taking into account an individual's liking may help dietitians and
406 practitioners provide effective dietary counseling while supporting individual
407 preference. In addition, our results may help to guide effective targeted measures in
408 prevention. For instance, sensory education measures tailored to individual liking
409 could provoke a shift in liking toward more complex foods in persons who strongly
410 favor fatty foods, thereby leading to reduced acceptance of fatty-salted or fatty-
411 sweetened foods and greater dietary variety [51]. Indeed, previous works
412 demonstrated that the preferred amounts of fat, salt and sugar in foods have an

413 innate basis that can be changed by modifying the frequency of sensory exposure to
414 the fatty, salty and sweet tastes [52-54]. Another potential alternative would be to
415 reduce content of fats, sugar and salt of industrialized products while maintaining the
416 same consumer appreciation and pleasantness by encouraging more technical and
417 commercial innovation.

418 **List of abbreviations**

419 BMI: body mass index

420 HR: hazard ratio

421 M: men

422 RD: reduction of deviance

423 RHR: reduction in hazard ratio

424 W: women

425 **Ethics approval and consent to participate**

426 This study was conducted according to guidelines laid down in the Declaration of
427 Helsinki, and all procedures were approved by the Institutional Review Board of the
428 French Institute for Health and Medical Research (IRB Inserm
429 n°0000388FWA00005831) and the “Commission Nationale Informatique et Libertés”
430 (CNIL n°908450 and n°909216). Electronic informed consent was obtained from all
431 subjects. This study is registered in EudraCT (n°2013-000929-31).

432 **Competing interests**

433 The authors declare that they have no competing interest.

434 **Authors' contributions**

435 AL: conducted the literature review and drafted the manuscript; AL: performed
436 analyses; SA, KC, AD, PS, SP, LF, SH and CM: were involved in the interpretation of
437 results and critically reviewed the manuscript; and SH and CM: were responsible for
438 the development of the design and the protocol of the study. All authors read and
439 approved the final manuscript.

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Table 1: Baseline characteristics of subjects who developed a CMD or not during the follow-up, NutriNet-Santé cohort, 2010-2016, France

	Cardiovascular diseases			Diabetes			Hypertension		
	Healthy participants n=40667	Cases n=655	P	Healthy participants n=40980	Cases n=342	P	Healthy participants n=36029	Cases n=1907	P
<i>General characteristics</i>									
Age, y	44.4 ± 14.2	59.4 ± 11.1	<0.0001	44.6 ± 14.3	56.2 ± 10.2	<0.0001	42.7 ± 13.7	55.8 ± 11.7	<0.0001
Sex, % women	78.0	52.2	<0.0001	77.7	59.9	<0.0001	79.3	66.3	<0.0001
BMI, kg/m ²	23.7 ± 4.4	25.1 ± 1.3	<0.0001	23.7 ± 4.3	30.2 ± 6.3	<0.0001	23.3 ± 4.1	25.8 ± 4.8	<0.0001
Educational level, %			<0.0001			<0.0001			<0.0001
Elementary school	2.8	5.0		2.8	4.1		2.4	5.1	
Secondary school	33.5	43.4		33.5	48.5		31.9	42.0	
College graduate	30.6	24.4		30.5	23.4		31.2	26.5	
Advanced degree	32.5	26.0		32.5	22.5		33.9	25.3	
Other	0.6	1.2		0.7	1.5		0.6	1.1	
Smoking status, %			<0.0001			<0.0001			<0.0001
Never-smoker	48.5	35.4		48.3	35.4		49.0	43.1	
Former smoker	35.3	51.2		35.5	50.3		34.0	44.9	
Current smoker	16.2	13.4		16.2	14.3		17.0	12.0	
Physical activity, %			0.0003			0.01			<0.0001
Low	29.7	37.4		29.8	28.1		29.0	35.4	
Moderate	38.8	36.0		38.8	35.1		39.2	35.8	
High	23.3	19.4		23.2	30.4		23.5	21.7	
Missing data	8.2	7.2		8.2	6.4		8.3	7.1	
Family history of myocardial infarction, %	11.2	22.0	<0.0001	11.3	18.1	<0.0001	10.1	17.3	<0.0001
Family history of stroke, %	11.7	20.9	<0.0001	11.8	19.9	<0.0001	10.5	18.2	<0.0001
Family history of diabetes, %	13.5	14.1	0.68	13.3	33.0	<0.0001	13.3	17.7	<0.0001
Family history of hypertension, %	32.0	40.3	<0.0001	32.1	40.6	0.0007	28.7	41.6	<0.0001
<i>Sensory liking scores</i>									
Liking for fat-and-salt	4.00 ± 1.4	3.80 ± 1.4	0.0003	4.00 ± 1.4	4.17 ± 1.3	0.02	4.02 ± 1.4	3.83 ± 1.4	<0.0001
Liking for fat-sweet	3.85 ± 1.8	3.25 ± 1.6	<0.0001	3.84 ± 1.8	3.75 ± 1.7	0.33	3.91 ± 1.8	3.46 ± 1.7	<0.0001
Liking for sweet	3.80 ± 1.3	3.65 ± 1.3	0.006	3.80 ± 1.3	3.57 ± 1.3	0.002	3.81 ± 1.3	3.67 ± 1.3	<0.0001
Liking for salt	3.73 ± 1.6	3.88 ± 1.6	0.19	3.79 ± 1.6	4.14 ± 1.6	<0.0001	3.80 ± 1.6	3.67 ± 1.5	0.004
<i>Food group consumption, g/d</i>									
Fruits	262 ± 183	304 ± 189	<0.0001	262 ± 184	255 ± 171	0.45	259 ± 183	290 ± 193	0.45
Vegetables	222 ± 128	239 ± 136	0.001	223 ± 128	228 ± 128	0.44	220 ± 128	239 ± 129	<0.0001
Meat	46 ± 46	48 ± 45	0.27	46 ± 46	64 ± 52	<0.0001	45 ± 45	52 ± 46	<0.0001

Processed meat	33 ± 34	34 ± 36	0.16	33 ± 34	41 ± 36	<0.0001	32 ± 34	33 ± 34	0.30
Fish	43 ± 48	53 ± 51	<0.0001	43 ± 48	54 ± 55	0.0002	42 ± 48	49 ± 49	<0.0001
Milk and yogurts	169 ± 158	164 ± 150	0.48	168 ± 158	174 ± 164	0.50	168 ± 159	178 ± 157	0.006
Cheese	37 ± 31	37 ± 30	0.96	37 ± 31	43 ± 33	0.002	37 ± 31	38 ± 37	0.18
Butter and other added fats	14 ± 14	15 ± 16	0.0005	14 ± 14	16 ± 16	0.0009	14 ± 14	14 ± 14	0.02
Oil	9 ± 9	9 ± 10	0.60	9 ± 9	9 ± 9	0.91	9 ± 9	9 ± 9	0.79
Salted snacks and appetizers	6 ± 12	5 ± 11	0.63	6 ± 12	6 ± 13	0.78	6 ± 12	5 ± 11	0.0007
Savory sauces	18 ± 18	17 ± 17	0.17	18 ± 18	20 ± 20	0.01	18 ± 18	17 ± 18	0.38
Starchy foods	188 ± 105	202 ± 118	0.0006	188 ± 105	218 ± 117	<0.0001	187 ± 104	196 ± 115	0.0003
Whole grain products	33 ± 50	34 ± 46	0.77	33 ± 50	30 ± 44	0.30	33 ± 50	34 ± 51	0.56
Sugar and sugary products	22 ± 25	25 ± 26	0.002	22 ± 25	17 ± 23	<0.0001	22 ± 25	23 ± 25	0.04
Fatty-sweet products	71 ± 64	58 ± 58	<0.0001	71 ± 64	61 ± 62	0.003	73 ± 65	59 ± 59	<0.0001
Sweetened cream desserts	36 ± 55	32 ± 55	0.10	36 ± 55	32 ± 50	0.18	36 ± 56	32 ± 53	0.001
Sweetened soft drinks	45 ± 107	27 ± 73	<0.0001	44 ± 107	38 ± 110	0.28	47 ± 110	30 ± 82	<0.0001
Alcoholic beverages	102 ± 162	154 ± 197	<0.0001	102 ± 162	146 ± 204	<0.0001	98 ± 159	131 ± 187	<0.0001
Energy, kcal/d	1901 ± 511	1970 ± 508	0.0005	1901 ± 511	2015 ± 526	<0.0001	1901 ± 511	1930 ± 523	0.02

¹ P values are for the comparison between subjects with illness and those who not and were determined by using Student's t-test or chi-square test as appropriate.

² Mean ± SD (all such values)

Table 2: Associations between liking for fat-and-salt and risk of cardiovascular disease from multivariable Cox proportional hazards model

Cardiovascular disease n=41,322				
	HR ¹ (95% CI)	P	RHR% ²	RD% ³
Liking for fat-and-salt				
Base model (sex and age adjusted)	1.10 (1.02;1.19)	0.01		
M2 Adjusted model ⁴	1.08 (1.00;1.16)	0.04		35
M3 Model assessing the mediating effect of dietary intake ⁵	1.07 (0.99;1.15)	0.11	30	61
M4 Model assessing the mediating effect of body mass index ⁶	1.06 (0.98;1.14)	0.16	40	70

¹ Hazard ratio and 95% confidence interval

² % RHR: percentage reduction in HR by inclusion of mediator $((\text{HR base model} - \text{HR base model} + \text{mediator}) / (\text{HR base model} - 1)) * 100$

³ % RD: percentage of sensory liking reduction in deviance explained by inclusion of mediator and confounders $((\text{reduction in deviance due to sensory liking of base model}) - (\text{reduction in deviance due to sensory liking of base model} + \text{mediator and confounders}) / \text{RD due to sensory liking of base model}) * 100$

⁴ M2: adjusted model: M1 + educational level, alcohol consumption, smoking status, physical activity and family medical history (family history of stroke and myocardial infarction)

⁵ M3: model assessing the mediating effect of dietary intake: M2 + energy intake, month of inclusion and food groups intake (fruits, meat, processed meat, fish, salted snacks and appetizers, cheese, oil, butter and other added fats, starchy foods, whole grain products, sugar and sugary products)

⁶ M4: model assessing the mediating effect of body mass index: M3 + body mass index

Table 3: Associations between liking for fat-and-salt, fat-and-sweet, sweet and salt, and risk of type 2 diabetes from multivariable Cox proportional hazards model

Diabetes n=41,322				
	HR ¹ (95% CI)	P	RHR% ²	RD% ³
Liking for fat-and-salt				
Base model (sex and age adjusted)	1.30 (1.18;1.43)	<0.0001		
M2 Adjusted model ⁴	1.27 (1.15;1.41)	<0.0001		18
M3 Model assessing the mediating effect of dietary intake ⁵	1.15 (1.04;1.28)	0.009	50	75
M4 Model assessing the mediating effect of body mass index ⁶	1.08 (0.97;1.20)	0.16	73	93
Liking for fat-and-sweet				
Base model (sex and age adjusted)	1.09 (1.01;1.17)	0.02		
M2 Adjusted model	1.07 (0.99;1.15)	0.08		43
M3 Model assessing the mediating effect of dietary intake	1.06 (0.99;1.14)	0.10	33	50
M4 Model assessing the mediating effect of body mass index	1.04 (0.97;1.12)	0.30	56	80
Liking for sweet				
Base model (sex and age adjusted)	0.76 (0.69;0.84)	<0.0001		
M2 Adjusted model	0.78 (0.70;0.86)	<0.0001		23
M3 Model assessing the mediating effect of dietary intake	0.86 (0.77;0.95)	0.004	42	70
M4 Model assessing the mediating effect of body mass index	0.89 (0.80;0.99)	0.04	54	84
Liking for salt				
Base model (sex and age adjusted)	1.09 (1.01;1.18)	0.02		
M2 Adjusted model	1.08 (1.00;1.17)	0.04		16
M3 Model assessing the mediating effect of dietary intake	1.06 (0.98;1.14)	0.16	33	62
M4 Model assessing the mediating effect of body mass index	1.07 (0.99;1.16)	0.08	22	42

¹ Hazard ratio and 95% confidence interval

²% RHR: percentage reduction in HR by inclusion of mediator ((HR base model – HR base model + mediator) / (HR base model – 1))*100

³% RD: percentage of sensory liking reduction in deviance explained by inclusion of mediator and confounders ((reduction in deviance due to sensory liking of base model) – (reduction in deviance due to sensory liking of base model + mediator and confounders) / RD due to sensory liking of base model)*100

⁴ M2: adjusted model: M1 + educational level, alcohol consumption, smoking status, physical activity and family medical history of diabetes

⁵ M3: model assessing the mediating effect of dietary intake: M2 + energy intake, month of inclusion and food groups intake (fruits, vegetables, meat, processed meat, savory sauces, cheese, butter and other added fats, starchy foods, whole grain products, sugar and sugary products, sweetened soft drinks)

⁶ M4: model assessing the mediating effect of body mass index= M3 + body mass index

Table 4: Associations between liking for fat-and-salt and risk of hypertension from multivariable Cox proportional hazards model

Hypertension n=37,936				
	HR ¹ (95% CI)	P	RHR% ²	RD% ³
Liking for fat-and-salt				
Base model (sex and age adjusted)	1.08 (1.04;1.13)	0.0002		
M2 Adjusted model ⁴	1.07 (1.03;1.12)	0.001		24
M3 Model assessing the mediating effect of dietary intake ⁵	1.05 (1.00;1.10)	0.04	38	68
M4 Model assessing the mediating effect of body mass index ⁶	1.01 (0.97;1.06)	0.57	88	98

¹ Hazard ratio and 95% confidence interval

² % RHR: percentage reduction in HR by inclusion of mediator $((\text{HR base model} - \text{HR base model} + \text{mediator}) / (\text{HR base model} - 1)) * 100$

³ % RD: percentage of sensory liking reduction in deviance explained by inclusion of mediator and confounders $((\text{reduction in deviance due to sensory liking of base model}) - (\text{reduction in deviance due to sensory liking of base model} + \text{mediator and confounders}) / \text{RD due to sensory liking of base model}) * 100$

⁴ M2: adjusted model: M1 + educational level, alcohol consumption, smoking status, physical activity and family medical history of hypertension

⁵ M3: model assessing the mediating effect of dietary intake: M2 + energy intake, month of inclusion and food groups intake (fruits, vegetables, meat, processed meat, savory sauces, milk and yogurts, oil, starchy foods, whole grain products, sugar and sugary products)

⁶ M4: model assessing the mediating effect of body mass index: M3 + body mass index

