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Sweetened beverages are associated with a higher risk of differentiated thyroid cancer in the EPIC cohort. A dietary pattern approach.

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Abbreviations: BMI, body mass index; DQ, dietary questionnaire; EPIC, European Prospective Investigation into Cancer and Nutrition; TC, thyroid cancer

1 **ABSTRACT:**

2 Background. Dietary-pattern analysis has gained particular interest because it
3 reflects the complexity of dietary intake. The aim of this study was to explore the
4 associations between *a posteriori* dietary patterns, derived using a data-driven
5 approach, and the risk of differentiated thyroid cancer (TC) in Europe.

6 Methods. This investigation included 450,064 adults from the European Prospective
7 Investigation into Cancer and Nutrition (EPIC) cohort. Dietary intake was assessed
8 using validated country-specific dietary questionnaires. *A posteriori* dietary patterns
9 were computed using principal component analyses. Cox regression was used to
10 calculate multivariable adjusted hazard ratios (HRs) and 95% confidence intervals
11 (CIs).

12 Results. After a mean follow-up time of 14 years, 712 first differentiated TCs were
13 diagnosed. In the fully adjusted model, a dietary pattern characterized by alcohol
14 consumption (basically beer and wine) was negatively associated with differentiated
15 TC risk ($HR_{Q4vs.Q1}=0.75$; 95%CI:0.60 to 0.94, P-trend=0.005), while a dietary pattern
16 rich in sweetened beverages was positively associated with differentiated TC risk
17 ($HR_{Q4vs.Q1}=1.26$; 95%CI:0.99 to 1.61; P-trend=0.07). The remaining 8 dietary
18 patterns were not related to differentiated TC risk. The intake of sweetened
19 beverages was positively associated with differentiated TC risk ($HR_{100mL/d}=1.05$;
20 95%CI:1.00 to 1.11), especially with papillary TC risk ($HR_{100mL/d}=1.07$; 95%CI:1.01
21 to 1.13). Similar results were observed with sugary and artificially sweetened
22 beverages.

23 Conclusions. The investigation of dietary patterns detected that the consumption of
24 sweetened beverages was associated with a higher risk of differentiated thyroid

25 cancer. Our results are in line with the general dietary recommendations of reducing
26 the consumption of sweetened beverages.

27

28 INTRODUCTION

29 Thyroid cancer (TC) is the most common endocrine cancer worldwide [1]. Its
30 incidence has been growing steadily in the last 3 decades, mainly due to the
31 increasing over-diagnosis [2], but also due to changes in dietary and lifestyle factors
32 [3].

33 Recently, several prospective studies have investigated the potential role of
34 individual nutrients, foods, and food groups in thyroid carcinogenesis [4, 5]. In
35 particular, within the European Prospective Investigation into Cancer and Nutrition
36 (EPIC) cohort, negative associations were observed with polyunsaturated fatty acids
37 and alcohol consumption [6]; and positive associations with the intake of total
38 energy, sugar and glycaemic index [7]. Regarding foods, null results have been
39 generally found with fish [8], fruits and vegetables [9], tea and coffee [10]
40 consumption. However, people consume combinations of foods rather than single
41 foods or nutrients. Likewise, dietary patterns allow taking into account the cumulative
42 and interactive effects of foods and nutrients. Two approaches are usually
43 considered for defining dietary patterns: i) the *a priori* or hypothesis-oriented
44 approach (e.g., Mediterranean diet and Healthy Eating Index); and ii) the *a posteriori*
45 or exploratory approach, applying data-driven statistical methods, such as principal
46 component, factor and cluster analysis [11].

47 To our knowledge, only four small case-control studies have evaluated the
48 association between *a posteriori* dietary patterns and TC risk, showing that in Greece
49 and in the USA, dietary patterns rich in raw vegetables and fresh fruit [12, 13], as
50 well as a traditional Polynesian dietary pattern in French Polynesia [14] were
51 inversely related to TC risk. In contrast, adherence to a western dietary pattern was

52 associated with a higher differentiated TC risk in an Iranian study [15]. However,
53 associations between *a posteriori* dietary patterns and TC risk have not been
54 investigated in prospective studies yet. Therefore, our aim was to explore these
55 relationships in the EPIC cohort, a prospective and large multicentre European
56 study, with a high diversity in the consumption of food groups and dietary patterns
57 [16].

58

59 **MATERIAL AND METHODS**

60 **Study population**

61 The EPIC study is an on-going multinational cohort designed to investigate the
62 relation between diet, lifestyle, and cancer risk. The cohort consists of 521,324 men
63 and women, mostly aged 35-70 years, recruited between 1992 and 2000,
64 predominantly from the general population of 10 European countries (Denmark,
65 France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden, and the
66 United Kingdom) [17]. The study was approved by the ethical review boards from
67 the International Agency for Research on Cancer and from all local centres.
68 Moreover, all participants provided written informed consent. Individuals with cancer
69 diagnoses other than non-melanoma skin cancer before recruitment (n=25,184),
70 those with missing information on date of diagnosis or incomplete follow-up data (n
71 = 4,148), those with lacking information on lifestyle factors (n = 1,277), those with
72 missing dietary data or in the highest or lowest 1% of the distribution for the ratio of
73 energy intake to estimated energy requirement (n = 14,555), and participants from
74 Greece (n=26,044), who did not provide data for this study, were excluded from
75 analyses.

76 **Data collection**

77 Dietary and lifestyle data were collected at baseline and have been described
78 previously [17]. Briefly, the usual diet of the previous year was assessed through a
79 validated centre/country-specific dietary questionnaire (*i.e.*, quantitative dietary
80 questionnaires, semi-quantitative food-frequency questionnaires, or a combination
81 of diet record and food-frequency questionnaires). Foods were primarily classified
82 according to a common classification into 17 groups and 124 subgroups [18] and
83 reclassified in our analyses into 36 main food subgroups, listed in **Table 1**.
84 Sweetened beverages included carbonated/soft/isotonic drinks and diluted syrups
85 and are divided into sugary and artificially sweetened beverages. Some EPIC
86 centres did not collect data on sugary sweetened beverages (Asturias, Florence,
87 Granada, Murcia, Navarra, Ragusa, San Sebastian, Turin, Umea, and Varese) or on
88 artificially sweetened beverages (Florence, Ragusa, Turin, Umea, and Varese).
89 Total energy and nutrient intakes were estimated by using the standardized EPIC
90 Nutrient Database [19]. Lifestyle questionnaires were used to collect data on lifetime
91 and current smoking status, physical activity classified according to the Cambridge
92 Physical Activity Index [20], education, menstrual and reproductive history. Height
93 and weight were measured in most centres, except in Oxford (UK), Norway and
94 France, where anthropometric measurements were self-reported [17].

95 **Follow-up and ascertainment of thyroid cancer cases**

96 Cancer incidence was determined through record linkage with national and regional
97 cancer registries or via a combination of methods, including the use of health
98 insurance records, contacts with cancer and pathology registries, and active follow-
99 up evaluation of study participants and their next of kin. Primary incident TC cases

100 were defined using the 10th Revision of the International Classification of Diseases
101 (ICD-10 code C73). After excluding at baseline 52 poorly differentiated TC (*i.e.*,
102 anaplastic (n = 9), medullary (n = 37), lymphoma (n = 1), or “other morphologies” (n
103 = 5)); 712 differentiated TC (*i.e.*, papillary (n=573), follicular (n=108), and not
104 otherwise specified TC (n=31)) were included in our analyses.

105 **Statistical Analyses**

106 Baseline characteristics were tabulated in cases and all cohort participants using
107 mean (SD) or median (25th and 75th percentiles) for continuous variables and n (%)
108 for categorical variables.

109 Dietary patterns derived from 36 food subgroups were computed using principal
110 component analysis. Independence of scale of the variances and co-variances was
111 achieved by applying the squared root of the food subgroups. Log and square-root
112 transformations were considered but the large number of non-consumers required
113 the use of the square-root. We retained the first 10 components that explained
114 almost 80% of the total cumulative variance. The principal component loadings
115 represent how much a food subgroup contributes to a dietary pattern. Each principal
116 component was interpreted (“named”) based on the food subgroups that had
117 absolute loadings $\geq|0.50|$.

118 Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between
119 dietary patterns and differentiated TC risk were obtained from stratified Cox
120 proportional hazard models using age as the underlying time scale. Age at entry was
121 defined as the participants’ age at recruitment, and exit time was age at diagnosis of
122 thyroid cancer, death, loss to follow-up or censoring at the end of the follow-up
123 period, whichever came first. The proportional hazards assumption was evaluated

124 in all models using tests and graphical diagnostics based on the Schoenfeld
125 residuals, and no evidence of violation was detected. The factor scores of the dietary
126 patterns were included in the Cox regressions as quartiles or continuously. P-trends
127 were calculated by assigning ordinal numbers 1 to 4 according to the participant's
128 quartile of intake. The basic model was stratified by sex, centre, and age at
129 recruitment (1y interval). The fully adjusted model was additionally adjusted for
130 potential confounders selected *a priori* [21, 22]: body mass index (BMI; kg/m²),
131 smoking status (never, former, current, and not specified), physical activity (inactive
132 or moderately inactive, active or moderately active, and not specified), educational
133 level (primary or lower; secondary or higher, and not specified), and total energy
134 (kcal/d) intake and in women also for menopausal status (premenopausal,
135 perimenopausal, postmenopausal, surgical menopause), oral contraceptive use and
136 infertility problems. Similar Cox models were also computed to evaluate the
137 association between total, sugary, and artificially sweetened beverages and
138 differentiated TC risk, and its main histological subtypes (papillary and follicular
139 tumours). The fully adjusted model for sweetened beverages was further adjusted
140 for alcohol intake (g/d). Alcohol intake was not included in the Cox models assessing
141 dietary patterns because dietary patterns included alcoholic beverages. The Wald
142 test was used to assess the heterogeneity of risk between TC subtypes (papillary
143 vs. follicular tumours). Similar models were computed to check the variability
144 between countries with a high vs. low TC incidence. EPIC countries with TC
145 incidence rates per year of >1/10,000 in women (i.e., France, Germany, Italy, and
146 Spain) were considered to have a high TC incidence. Moreover, interactions
147 between sweetened beverages and sex and BMI (<25, 25-30, >30kg/m²) in relation

148 to differentiated TC risk were computed. Sex and BMI were previously identified as
149 potential modifiers of the association with sugar intake, the most relevant nutrient in
150 sweetened beverages [7]. A sensitivity analysis was performed excluding 76 cases
151 who were diagnosed with TC within the first 2 years of follow-up, because some
152 participants may have modified their diet during the prediagnostic period of the
153 disease. All P values presented are 2-tailed and were considered to be statistically
154 significant when $P < 0.05$. All statistical analyses were conducted using R 3.2.1
155 software (R Foundation for Statistical Computing, Vienna, Austria).

156

157 **RESULTS**

158 Overall, 450,064 participants (70.8% women) were included in the current analysis.
159 During a mean (SD) follow-up of 13.9 (4.0) years, 712 (89.6% women) first incident
160 differentiated TC cases were identified, including 573 papillary and 108 follicular
161 tumours (**Supplementary figure 1**). Differentiated TC cases were more likely to be
162 slightly younger, women, and never smokers, and to consume less alcohol and do
163 less physical activity compared to all participants (**Table 2**).

164 The first 10 principal components derived from the whole cohort principal component
165 analysis are shown in **Table 1**, including the factor loadings of the 36 food
166 subgroups. The first five dietary patterns are characterized by the consumption of a
167 single food group: 1st component with tea, 2nd component with coffee, 3rd component
168 with alcoholic beverages (beer and wine), 4th component with sweetened beverages,
169 and 5th component with milk and dairy products. The first 5 and 10 principal
170 components explained almost 60% and 80%, respectively, of the total accumulated
171 variance.

172 In the fully adjusted model, dietary pattern 3 (beer and wine) was inversely
173 associated with differentiated TC risk ($HR_{Q4vs.Q1}=0.75$; 95%CI: 0.60 to 0.94; P-trend
174 = 0.005) (**Table 3**). Higher adherence to dietary pattern 4 (sweetened beverages)
175 was borderline positively associated with differentiated TC risk ($HR_{Q4vs.Q1}=1.26$;
176 95%CI: 0.99 to 1.61; P-trend = 0.07). The remaining dietary patterns were not related
177 to differentiated TC risk. Similar HRs were observed in papillary and follicular TCs,
178 and in countries with high and low TC incidence (data not shown).

179 In further analyses, we investigated the associations between the major food groups
180 of the principal components 3 and 4 and differentiated TC risk. Associations with
181 alcoholic drinks (principal component 3) were evaluated in this cohort previously [6].
182 Sweetened beverages (principal component 4) were significantly and positively
183 associated with differentiated TC risk in model 1 and model 2 ($HR_{100mL/d}=1.05$;
184 95%CI: 1.00 to 1.11) (**Table 4**). In the sensitivity analysis, after excluding 76 TC
185 cases diagnosed in the first two years of follow-up, results were similar
186 ($HR_{100mL/d}=1.06$; 95%CI: 1.01 to 1.12). No statistically significant interactions were
187 observed for total sweetened beverage intake and differentiated TC risk according
188 to either sex (P for interaction = 0.08) or BMI (P for interaction = 0.49). Results for
189 sugary and artificially sweetened beverages were broadly along the same line as
190 those for total sweetened beverages, although they were not statistically significant
191 (**Table 4**).

192 When investigating by TC subtype, total sweetened beverages were positively
193 associated with papillary TC risk ($HR_{100mL/d}=1.07$; 95%CI: 1.01 to 1.13)
194 (**Supplementary table 1**). Similar results, but not statistically significant, were found
195 for sugary ($HR_{100mL/d}=1.08$; 95%CI: 0.99 to 1.17) and artificially ($HR_{100mL/d}=1.05$;

196 95%CI: 0.95 to 1.15) sweetened beverages and papillary TC risk. Total sweetened
197 beverages, and subtypes, were not related to follicular TC risk; although, no
198 statistically significant differences were observed between papillary and follicular
199 thyroid tumours.

200

201 **DISCUSSION**

202 In the present study, a dietary pattern characterized by consumption of low alcoholic
203 beverages (wine and beer) was associated with a lower risk of differentiated TC,
204 while a dietary pattern rich in sweetened beverages tended to be associated with a
205 higher differentiated TC risk. Indeed, the consumption of sweetened beverages was
206 related to a higher risk of differentiated TC risk, especially papillary tumours.

207 In our study, dietary pattern 3, characterized by wine and beer consumption, was
208 associated with a lower risk of differentiated TC. Likewise, a meta-analysis including
209 33 observational studies also found that alcohol consumption was associated with a
210 lower TC risk [23], especially with light/moderate alcohol consumption (up to 1 drink
211 for women and up to 2 drinks for men) [24]. In a previous EPIC investigation, similar
212 results with both moderate baseline and lifetime alcohol intake, especially with wine
213 and beer, were observed [6]. Although the epidemiological evidence seems to be
214 consistent, the underpinning mechanism of the role of moderate alcohol intake in
215 thyroid carcinogenesis is still unknown.

216 A dietary pattern rich in sweetened drinks (dietary pattern 4) tended to be associated
217 with a higher risk of differentiated TC. Further investigation in our study showed that
218 there was a statistically significant positive relationship between the intake of
219 sweetened beverages, as a food subgroup, and differentiated TC risk, particularly

220 with papillary TC (the most common TC). To our knowledge, this is the first study
221 assessing this relationship, although similar associations were previously observed
222 with fruit juices in the EPIC study [9]. Moreover, we previously found positive
223 associations of differentiated TC with total energy and sugar intake, and glycaemic
224 index [7]. It is important to bear in mind that sugary sweetened beverages, and to a
225 lesser extent fruit juices, are rich in sugars and empty calories. Diets rich in sugary
226 sweetened beverages are also associated with a higher risk of obesity [25] and type
227 2 diabetes [26], which are well-known risk factors for TC [27, 28]. Furthermore,
228 overweight/obesity is a main determinant of insulin resistance, hyperinsulinemia,
229 and therefore type 2 diabetes [29]. All these factors increase inflammation [30] and
230 oxidative stress [31] that are also related to an increased risk of TC. Likewise, sugary
231 sweetened beverages are the main food source of fructose, which may promote
232 weight gain in part due to excess calories, adverse glycaemic response, an increase
233 of the hepatic lipogenesis, and a greater accumulation of visceral and ectopic fat
234 [32]. Therefore, sugar and sugary drinks, such as soft drinks and fruit juices, may
235 increase differentiated TC risk through these mechanisms.

236 We also investigated differences between sugary vs. artificially sweetened
237 beverages in relation to differentiated TC risk. The results were similar indicating
238 potentially analogous harmful effects of both types of sweetened beverages, for
239 example in 24-h glucose profiles [33]. Several studies have observed that artificially
240 sweetened beverages are associated with a higher risk of type 2 diabetes [34],
241 obesity [25, 35] cardiovascular diseases [36], and all-cause mortality [37]. Despite
242 the epidemiological evidence, further mechanistic studies are warranted to
243 understand the effect of artificially sweetened beverages in thyroid carcinogenesis,

244 particularly papillary thyroid tumours. On one hand, people drinking artificially
245 sweetened beverages may have similar unhealthy dietary and lifestyle habits as
246 those drinking sugary sweetened beverages [37]. On the other hand, artificial
247 sweeteners may also have harmful effects by themselves: increasing sweet
248 preferences, altering appetite responses, gut microbiota, gut hormone release and,
249 subsequently, the carbohydrate metabolism [38].

250 In the current study, none of the remaining *a posteriori* generated dietary patterns
251 were related to differentiated TC risk. Dietary patterns 1 and 2 were rich in tea and
252 coffee, respectively, and these beverages were not associated with differentiated TC
253 risk in preceding analyses in the EPIC study [10]. Dietary pattern 5 was rich in dairy
254 products, the consumption of which have been mostly not associated with TC risk
255 [5]. Dietary pattern 8 was mainly rich in fruits and vegetables, but it was not
256 associated with differentiated TC risk either. Identical results were observed with fruit
257 and vegetable consumption in the EPIC study [9]. However, protective results were
258 detected in two previous small case-control studies with diets rich in fruits and
259 vegetables [13] or a traditional Polynesian diet (characterized by a high consumption
260 of fish and shellfish, banana, citrus and tropical fruits, coconut water, uru (breadfruit),
261 tubers, and dairy products) [14].

262 Strengths of this study included the prospective design, the relatively large number
263 of TC cases (although the number of cases is limited for follicular tumours), the
264 completeness of follow-up and dietary questionnaires and the inclusion of
265 participants from cohorts across nine European countries with widely heterogeneous
266 dietary habits. Limitations of our study were the measurement error in the dietary
267 questionnaires, although these were validated and centre/country specific [17]. In

268 our study, we distinguished between sugary and artificially sweetened beverages;
269 however, in the nineties (study baseline) the consumption of artificially sweetened
270 beverages was relatively low (<25% of total soft drinks) and the results with artificially
271 sweetened beverages may be affected by reverse causation [39]. Modifications
272 during the follow-up in diet and lifestyle factors cannot be considered in this study
273 since we have only available data at baseline. Though we have adjusted our models
274 for several important indicators of healthy lifestyle, the presence of possible residual
275 confounding cannot be excluded.

276 In the current study, a dietary pattern moderate in alcohol consumption was
277 associated with a lower differentiated TC risk, strengthening the previous results in
278 EPIC with single foods [6]. Moreover, a high adherence to a dietary pattern rich in
279 sweetened beverages tended to be related to a higher differentiated TC risk.
280 Likewise, the consumption of sweetened beverages was positively associated with
281 the risk of differentiated TC, especially papillary tumours, although further studies
282 are warranted to confirm this relationship. Our findings support the current public
283 health recommendations to reduce the consumption of sweetened beverages,
284 especially those rich in sugar but also those artificially sweetened, in order to
285 decrease the risk of developing differentiated TC, as well as other chronic diseases
286 (such as obesity, type 2 diabetes, other cancer types, and cardiovascular diseases)
287 [34, 40-42].

288

289 **ETHICS DECLARATIONS**

290 **Conflict of interest**

291 The authors are not aware of any conflicts of interest. DISCLAIMER: Where authors
292 are identified as personnel of the International Agency for Research on Cancer /
293 World Health Organization, the authors alone are responsible for the views
294 expressed in this article and they do not necessarily represent the decisions, policy
295 or views of the International Agency for Research on Cancer / World Health
296 Organization.

297 **Ethical approval**

298 This study was performed in line with the principles of the Declaration of Helsinki.
299 The study was approved by the ethical review boards from the International Agency
300 for Research on Cancer and from all participating EPIC centres.

301 **Consent to participate**

302 All participants provided written informed consent.

303 **AUTHORS' CONTRIBUTIONS:**

304 RZ-R, RC, AA designed the research; RZ-R obtained the fundings; VC, RC, MT
305 performed the statistical analyses and prepared the database; EW, MS, MA, M-CB-
306 R, AT, CK, VAK, CLC, GM, VK, GI, RT, LM, GS, EU-G, PA, M-DC, EA, SJ, LE, HF,
307 AKH, SR, AA provided data; RZ-R drafted the manuscript; RC, GB, EW, SR, AA
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320 **AVAILABILITY OF DATA AND MATERIALS:**

321 For information on how to apply for getting access to EPIC data and/or
322 biospecimens, please follow the instructions at <http://epic.iarc.fr/access/index.php>.

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- 503

504 Table 1. Score coefficients from a principal component analysis regarding foods or food groups consumed by the entire
 505 EPIC cohort, after a square root transformation.

Food group	Dietary Patterns									
	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
Potatoes	0.009	0.141	0.021	0.096	0.040	0.021	0.066	0.009	0.038	0.233
Leafy vegetables	-0.007	-0.137	-0.022	-0.128	0.072	-0.113	-0.096	0.054	0.089	0.037
Fruiting vegetables	0.011	-0.079	0.003	-0.059	0.057	-0.119	-0.150	0.135	0.113	-0.074
Root vegetables	0.059	0.024	-0.057	-0.006	-0.009	-0.048	-0.045	0.110	-0.056	-0.147
Cabbage	0.090	0.037	-0.043	-0.005	-0.036	-0.048	-0.060	0.095	-0.092	-0.223
Other vegetables	0.061	0.003	0.020	-0.100	0.022	-0.179	-0.020	0.072	-0.109	-0.003
Legumes	0.028	-0.078	-0.002	-0.028	0.034	-0.110	-0.025	0.040	-0.001	-0.015
Fruits	0.050	-0.175	-0.162	-0.128	0.067	-0.374	-0.338	0.621	0.237	-0.031
Nuts (spread) and seeds	0.018	0.006	0.013	-0.009	0.000	-0.014	-0.046	0.004	-0.006	-0.017
Other fruits	-0.027	-0.034	0.014	-0.002	0.007	0.001	-0.040	0.002	0.022	0.049
Milk and dairy products	0.162	0.173	-0.422	0.268	0.761	-0.215	0.011	-0.221	-0.012	-0.005
Cheese	-0.026	-0.018	0.016	-0.049	0.013	-0.029	-0.060	0.008	0.047	0.209
Pasta and rice	0.007	-0.093	0.041	-0.056	-0.033	-0.226	-0.045	0.039	-0.099	0.164
Bread	-0.045	0.006	0.063	-0.009	0.022	-0.007	-0.047	0.008	0.153	0.546
Other cereals	0.083	0.055	-0.031	0.080	0.011	-0.052	-0.019	0.048	-0.122	-0.201
Red meat	-0.026	0.042	0.046	-0.054	0.030	-0.096	0.025	-0.038	0.105	0.342
Poultry	-0.010	-0.024	0.012	-0.038	0.019	-0.092	0.002	-0.001	0.038	0.158
Processed meat	-0.056	0.037	0.053	0.036	0.032	0.040	-0.023	-0.047	0.090	0.284
Offal	0.001	-0.002	0.015	-0.032	0.015	-0.037	-0.004	-0.005	-0.002	0.072
Fish and shellfish	-0.031	-0.036	0.002	-0.048	0.036	-0.097	0.019	0.013	-0.041	0.095
Egg and egg products	-0.017	-0.001	0.018	-0.034	0.040	-0.050	-0.013	-0.013	0.028	0.131
Vegetable oils	0.010	-0.016	0.011	-0.016	0.005	-0.020	-0.026	-0.004	0.008	0.029
Olive oil	-0.034	-0.086	0.020	-0.033	0.008	-0.071	-0.018	0.017	0.035	0.075
Butter	0.017	0.009	0.014	-0.016	0.007	0.031	-0.039	-0.021	-0.001	0.047
Margarine	0.016	0.104	-0.009	0.086	0.008	0.058	0.021	0.007	0.026	0.038
Other fats	-0.022	0.007	0.003	0.015	-0.017	0.020	-0.006	-0.009	0.002	0.034
Sugar	0.028	0.067	0.007	0.032	0.007	-0.035	-0.016	0.001	0.045	0.274

Cake and biscuits	0.032	0.015	-0.034	0.053	0.004	0.056	-0.071	0.022	0.013	0.125
Fruit and vegetable juices	0.055	0.060	0.023	0.091	0.043	0.312	-0.763	-0.006	-0.503	0.142
Sweetened beverages	0.090	0.206	-0.045	0.657	-0.489	-0.413	-0.182	-0.141	0.153	-0.013
Coffee	-0.233	0.814	-0.260	-0.387	-0.133	-0.027	-0.057	0.105	0.048	-0.025
Tea	0.930	0.165	0.094	-0.204	-0.094	0.091	0.065	0.020	0.084	0.078
Herbal tea	-0.027	0.008	0.036	0.087	0.112	0.429	-0.321	-0.084	0.725	-0.185
Wine	-0.020	-0.005	0.330	-0.379	0.051	-0.407	-0.298	-0.599	0.079	-0.164
Beer	-0.058	0.328	0.762	0.227	0.335	-0.074	0.064	0.323	-0.030	-0.095
Other alcoholic beverages	0.008	0.035	0.065	-0.053	0.023	-0.066	-0.041	-0.072	0.026	-0.013
Explained variance (%)	18.5	17.5	9.0	7.6	6.3	5.4	5.1	4.3	3.3	2.4
Cumulative variance (%)	18.5	36.1	45.1	52.6	58.9	64.3	69.4	73.8	77.0	79.5

506 C= Component.

507 Table 2. Baseline characteristics of differentiated thyroid cancer (TC) cases and all
 508 cohort participants in the EPIC study.

Baseline characteristics	All N=450,064	TC Cases N=712
Age (y), mean (SD)	51.1 (9.8)	50.2 (7.9)
Sex, female (%)	70.8	89.6
Country, %		
France	14.9	34.8
Italy	9.9	17.8
Spain	8.9	11.2
United Kingdom	16.8	6.2
The Netherlands	8.1	2.4
Germany	10.8	11.5
Sweden	10.8	5.5
Denmark	12.2	5.5
Norway	7.6	5.1
Body mass index (kg/m ²), mean (SD)	25.3 (4.2)	25.1 (4.0)
Total energy intake (kcal/d), median (p25-p75)	1999 (1633-2437)	2005 (1648-2446)
Alcohol intake (g/d), median (p25-p75)	5.5 (0.9-15.2)	3.5 (0.5-11.7)
Smoking status (%)		
Never	48.7	55.9
Former	27.3	24.9
Current	22.2	16.9
Highest educational level, secondary or higher (%)	68.1	66.2
Physical activity, moderately active or active (%)	45.2	37.2
Menopausal status*, %		
Premenopausal	34.7	37.1
Perimenopausal	19.7	23.0
Postmenopausal	42.8	34.3
Surgical menopause	2.8	5.5
Ever use of hormone replacement therapy use*, yes (%)	25.2	25.2
Ever use of oral contraceptive use*, yes (%)	59.5	59.5
Infertility problems*, yes (%)	3.1	3.1

509 p25 and p75: percentile 25th and 75th.

510 *Only in women (n=318,647; 70.8%)

511 Missing values (classified as not specified): smoking status (n=8,421; 1.9%),
 512 education level (n=16,871; 3.7%), physical activity (n=8,824; 2.0%), ever use of
 513 hormonal replacement therapy (n=21,606; 6.8%), ever use of oral contraceptive
 514 (n=8,426; 2.6%), infertility problems (n=110,350; 34.6%)

515 P-values were from t-test, Wilcoxon test, or chi-square test as appropriate

516 Table 3. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of differentiated thyroid cancer according to
 517 sex-specific quartiles of dietary pattern score in the EPIC study.

Dietary pattern component	Quartile 1 HR (95%CI)	Quartile 2 HR (95%CI)	Quartile 3 HR (95%CI)	Quartile 4 HR (95%CI)	P-trend	Continuous HR (95%CI)	
C1	Model 1	1.00 (ref.)	1.13 (0.92 to 1.40)	1.39 (1.11 to 1.73)	1.04 (0.79 to 1.35)	0.20	1.00 (0.99 to 1.01)
	Model 2	1.00 (ref.)	1.15 (0.93 to 1.42)	1.42 (1.14 to 1.78)	1.08 (0.82, 1.41)	0.12	1.00 (0.99, 1.01)
C2	Model 1	1.00 (ref.)	0.98 (0.80 to 1.20)	1.02 (0.79 to 1.31)	1.01 (0.74 to 1.37)	0.91	1.00 (0.99 to 1.01)
	Model 2	1.00 (ref.)	0.98 (0.79 to 1.21)	1.01 (0.78 to 1.31)	1.00 (0.73 to 1.36)	0.96	1.00 (0.99 to 1.01)
C3	Model 1	1.00 (ref.)	0.83 (0.68 to 1.03)	0.70 (0.56 to 0.87)	0.74 (0.59 to 0.92)	0.003	0.98 (0.97 to 0.99)
	Model 2	1.00 (ref.)	0.84 (0.68 to 1.04)	0.71 (0.57 to 0.88)	0.75 (0.60 to 0.94)	0.005	0.98 (0.97 to 0.99)
C4	Model 1	1.00 (ref.)	1.07 (0.87 to 1.31)	1.11 (0.89 to 1.38)	1.28 (1.00 to 1.62)	0.06	1.02 (1.00 to 1.03)
	Model 2	1.00 (ref.)	1.06 (0.86 to 1.30)	1.10 (0.89 to 1.37)	1.26 (0.99 to 1.61)	0.07	1.02 (1.00 to 1.03)
C5	Model 1	1.00 (ref.)	1.02 (0.82 to 1.27)	0.99 (0.80 to 1.24)	1.01 (0.80 to 1.26)	0.98	1.00 (0.98 to 1.01)
	Model 2	1.00 (ref.)	1.03 (0.82 to 1.28)	1.00 (0.80 to 1.26)	1.03 (0.81 to 1.30)	0.89	1.00 (0.98 to 1.01)
C6	Model 1	1.00 (ref.)	0.98 (0.80 to 1.21)	1.00 (0.81 to 1.24)	1.06 (0.83 to 1.36)	0.69	1.00 (0.99 to 1.02)
	Model 2	1.00 (ref.)	0.99 (0.80 to 1.22)	1.01 (0.80 to 1.26)	1.07 (0.82 to 1.39)	0.64	1.00 (0.98 to 1.02)
C7	Model 1	1.00 (ref.)	1.03 (0.84 to 1.27)	0.92 (0.74 to 1.14)	0.97 (0.77 to 1.21)	0.53	1.00 (0.98 to 1.01)
	Model 2	1.00 (ref.)	1.02 (0.82 to 1.25)	0.89 (0.71 to 1.12)	0.93 (0.73 to 1.18)	0.36	0.99 (0.98 to 1.01)
C8	Model 1	1.00 (ref.)	0.98 (0.78 to 1.22)	1.13 (0.91 to 1.39)	1.07 (0.87 to 1.33)	0.31	1.01 (0.99 to 1.02)
	Model 2	1.00 (ref.)	0.97 (0.78 to 1.21)	1.12 (0.91 to 1.38)	1.06 (0.86 to 1.32)	0.37	1.01 (0.99 to 1.02)
C9	Model 1	1.00 (ref.)	0.95 (0.77 to 1.17)	0.88 (0.71 to 1.09)	0.87 (0.70 to 1.09)	0.18	0.99 (0.97 to 1.01)
	Model 2	1.00 (ref.)	0.94 (0.76 to 1.16)	0.86 (0.70 to 1.07)	0.86 (0.68 to 1.08)	0.13	0.99 (0.97 to 1.01)
C10	Model 1	1.00 (ref.)	1.09 (0.86 to 1.39)	1.09 (0.86 to 1.38)	1.09 (0.86 to 1.38)	0.56	1.01 (0.99 to 1.03)
	Model 2	1.00 (ref.)	1.10 (0.86 to 1.40)	1.11 (0.86 to 1.42)	1.14 (0.86 to 1.50)	0.42	1.01 (0.99 to 1.04)

518 C=Component

519 Model 1 was stratified by sex, centre, and age at recruitment

520 Model 2 was additionally adjusted for BMI, smoking status, physical activity, educational level, and energy intake, and in

521 women also for menopausal status, oral contraceptive use, and infertility problems

522 Table 4. Hazard ratios (HRs) and 95% confidence intervals (CIs) of the risk of differentiated thyroid cancer according to
 523 groups of sweetened beverage consumers in the EPIC study.

	Non-consumers	Tertile 1 of consumers	Tertile 2 of consumers	Tertile 3 of consumers	p-trend	Continuous (100mL/d)
Total sweetened beverages (mL/d)						
Intake	0	>0 - 28.6	28.7 - 107.5	>107.5 - 4201.7		
N of cases	393	122	113	84		712
Model 1	1.00 (ref)	1.11 (0.89 to 1.39)	1.20 (0.95 to 1.52)	1.21 (0.93 to 1.58)	0.08	1.06 (1.01 to 1.11)
Model 2	1.00 (ref)	1.11 (0.88 to 1.38)	1.19 (0.94 to 1.51)	1.17 (0.90 to 1.54)	0.13	1.05 (1.00 to 1.11)
Sugary sweetened beverages (mL/d) ¹						
Intake	0	>0 - 16.8	16.9 - 85.7	85.8 - 4201.7		
N of cases	337	56	63	39		495
Model 1	1.00 (ref)	0.96 (0.69 to 1.33)	1.20 (0.89 to 1.61)	0.96 (0.66 to 1.40)	0.68	1.08 (1.00 to 1.16)
Model 2	1.00 (ref)	0.97 (0.70 to 1.34)	1.18 (0.88 to 1.60)	0.91 (0.62 to 1.34)	0.86	1.06 (0.98 to 1.15)
Artificially sweetened beverages (mL/d) ¹						
Intake	0	>0 - 5.8	5.9 - 42.9	43.0 - 3389.5		
N of cases	392	29	32	42		495
Model 1	1.00 (ref)	0.89 (0.54 to 1.48)	0.87 (0.58 to 1.30)	1.26 (0.87 to 1.83)	0.12	1.02 (0.93 to 1.13)
Model 2	1.00 (ref)	0.88 (0.53 to 1.46)	0.83 (0.55 to 1.24)	1.16 (0.80 to 1.69)	0.26	1.00 (0.91 to 1.11)

524 Model 1 was stratified by sex, centre, and age at recruitment

525 Model 2 was additionally adjusted for BMI, smoking status, physical activity, educational level, alcohol and energy intake,
 526 and in women also for menopausal status, oral contraceptive use, and infertility problems

527 ¹Centres without data on sugary and artificially sweetened beverages were Asturias, Florence, Granada, Murcia, Navarra,
 528 Ragusa, San Sebastian, Turin, Umea, and Varese

529