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

ABSTRACT:

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

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

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

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

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

INTRODUCTION

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

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

To our knowledge, only four small case-control studies have evaluated the association between *a posteriori* dietary patterns and TC risk, showing that in Greece and in the USA, dietary patterns rich in raw vegetables and fresh fruit [12, 13], as well as a traditional Polynesian dietary pattern in French Polynesia [14] were inversely related to TC risk. In contrast, adherence to a western dietary pattern was associated with a higher differentiated TC risk in an Iranian study [15]. However, associations between *a posteriori* dietary patterns and TC risk have not been investigated in prospective studies yet. Therefore, our aim was to explore these relationships in the EPIC cohort, a prospective and large multicentre European study, with a high diversity in the consumption of food groups and dietary patterns [16].

MATERIAL AND METHODS

Study population

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

Data collection

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

Follow-up and ascertainment of thyroid cancer cases

Cancer incidence was determined through record linkage with national and regional cancer registries or via a combination of methods, including the use of health insurance records, contacts with cancer and pathology registries, and active follow-up evaluation of study participants and their next of kin. Primary incident TC cases were defined using the 10th Revision of the International Classification of Diseases (ICD-10 code C73). After excluding at baseline 52 poorly differentiated TC (*i.e.*, anaplastic (n = 9), medullary (n = 37), lymphoma (n = 1), or ‘‘other morphologies’’ (n = 5)); 712 differentiated TC (*i.e.*, papillary (n=573), follicular (n=108), and not otherwise specified TC (n=31)) were included in our analyses.

Statistical Analyses

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

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

Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between dietary patterns and differentiated TC risk were obtained from stratified Cox proportional hazard models using age as the underlying time scale. Age at entry was defined as the participants’ age at recruitment, and exit time was age at diagnosis of thyroid cancer, death, loss to follow-up or censoring at the end of the follow-up period, whichever came first. The proportional hazards assumption was evaluated in all models using tests and graphical diagnostics based on the Schoenfeld residuals, and no evidence of violation was detected. The factor scores of the dietary patterns were included in the Cox regressions as quartiles or continuously. P-trends were calculated by assigning ordinal numbers 1 to 4 according to the participant's quartile of intake. The basic model was stratified by sex, centre, and age at recruitment (1y interval). The fully adjusted model was additionally adjusted for potential confounders selected *a priori* [21, 22]: body mass index (BMI; kg/m^2), smoking status (never, former, current, and not specified), physical activity (inactive or moderately inactive, active or moderately active, and not specified), educational level (primary or lower; secondary or higher, and not specified), and total energy (kcal/d) intake and in women also for menopausal status (premenopausal, perimenopausal, postmenopausal, surgical menopause), oral contraceptive use and infertility problems. Similar Cox models were also computed to evaluate the association between total, sugary, and artificially sweetened beverages and differentiated TC risk, and its main histological subtypes (papillary and follicular tumours). The fully adjusted model for sweetened beverages was further adjusted for alcohol intake (g/d). Alcohol intake was not included in the Cox models assessing dietary patterns because dietary patterns included alcoholic beverages. The Wald test was used to assess the heterogeneity of risk between TC subtypes (papillary vs. follicular tumours). Similar models were computed to check the variability between countries with a high vs. low TC incidence. EPIC countries with TC incidence rates per year of >1/10,000 in women (i.e., France, Germany, Italy, and Spain) were considered to have a high TC incidence. Moreover, interactions between sweetened beverages and sex and BMI (<25, 25-30, >30kg/m^2) in relation to differentiated TC risk were computed. Sex and BMI were previously identified as potential modifiers of the association with sugar intake, the most relevant nutrient in sweetened beverages [7]. A sensitivity analysis was performed excluding 76 cases who were diagnosed with TC within the first 2 years of follow-up, because some participants may have modified their diet during the prediagnostic period of the disease. All P values presented are 2-tailed and were considered to be statistically significant when $P < 0.05$. All statistical analyses were conducted using R 3.2.1 software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

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

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

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

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

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

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

DISCUSSION

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

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

A dietary pattern rich in sweetened drinks (dietary pattern 4) tended to be associated with a higher risk of differentiated TC. Further investigation in our study showed that there was a statistically significant positive relationship between the intake of sweetened beverages, as a food subgroup, and differentiated TC risk, particularly with papillary TC (the most common TC). To our knowledge, this is the first study assessing this relationship, although similar associations were previously observed with fruit juices in the EPIC study [9]. Moreover, we previously found positive associations of differentiated TC with total energy and sugar intake, and glycaemic index [7]. It is important to bear in mind that sugary sweetened beverages, and to a lesser extent fruit juices, are rich in sugars and empty calories. Diets rich in sugary sweetened beverages are also associated with a higher risk of obesity [25] and type 2 diabetes [26], which are well-known risk factors for TC [27, 28]. Furthermore, overweight/obesity is a main determinant of insulin resistance, hyperinsulinemia, and therefore type 2 diabetes [29]. All these factors increase inflammation [30] and oxidative stress [31] that are also related to an increased risk of TC. Likewise, sugary sweetened beverages are the main food source of fructose, which may promote weight gain in part due to excess calories, adverse glycaemic response, an increase of the hepatic lipogenesis, and a greater accumulation of visceral and ectopic fat [32]. Therefore, sugar and sugary drinks, such as soft drinks and fruit juices, may increase differentiated TC risk through these mechanisms.

We also investigated differences between sugary vs. artificially sweetened beverages in relation to differentiated TC risk. The results were similar indicating potentially analogous harmful effects of both types of sweetened beverages, for example in 24-h glucose profiles [33]. Several studies have observed that artificially sweetened beverages are associated with a higher risk of type 2 diabetes [34], obesity [25, 35] cardiovascular diseases [36], and all-cause mortality [37]. Despite the epidemiological evidence, further mechanistic studies are warranted to understand the effect of artificially sweetened beverages in thyroid carcinogenesis, particularly papillary thyroid tumours. On one hand, people drinking artificially sweetened beverages may have similar unhealthy dietary and lifestyle habits as those drinking sugary sweetened beverages [37]. On the other hand, artificial sweeteners may also have harmful effects by themselves: increasing sweet preferences, altering appetite responses, gut microbiota, gut hormone release and, subsequently, the carbohydrate metabolism [38].

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

Strengths of this study included the prospective design, the relatively large number of TC cases (although the number of cases is limited for follicular tumours), the completeness of follow-up and dietary questionnaires and the inclusion of participants from cohorts across nine European countries with widely heterogeneous dietary habits. Limitations of our study were the measurement error in the dietary questionnaires, although these were validated and centre/country specific [17]. In our study, we distinguished between sugary and artificially sweetened beverages; however, in the nineties (study baseline) the consumption of artificially sweetened beverages was relatively low (<25% of total soft drinks) and the results with artificially sweetened beverages may be affected by reverse causation [39]. Modifications during the follow-up in diet and lifestyle factors cannot be considered in this study since we have only available data at baseline. Though we have adjusted our models for several important indicators of healthy lifestyle, the presence of possible residual confounding cannot be excluded.

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

ETHICS DECLARATIONS

Conflict of interest

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

Ethical approval

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

Consent to participate

All participants provided written informed consent.

AUTHORS' CONTRIBUTIONS:

RZ-R, RC, AA designed the research; RZ-R obtained the fundings; VC, RC, MT performed the statistical analyses and prepared the database; EW, MS, MA, M-CB-R, AT, CK, VAK, CLC, GM, VK, GI, RT, LM, GS, EU-G, PA, M-DC, EA, SJ, LE, HF, AKH, SR, AA provided data; RZ-R drafted the manuscript; RC, GB, EW, SR, AA largely contributed to the discussion. All authors reviewed, edited, and approved the final manuscript.

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AVAILABILITY OF DATA AND MATERIALS:

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

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

	Dietary Patterns									
Food group	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
Read 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

C= Component.

Table 2. Baseline characteristics of differentiated thyroid cancer (TC) cases and all 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

p25 and p75: percentile 25th and 75th.
*Only in women (n=318,647; 70.8%)
Missing values (classified as not specified): smoking status (n=8,421; 1.9%), education level (n=16,871; 3.7%), physical activity (n=8,824; 2.0%), ever use of hormonal replacement therapy (n=21,606; 6.8%), ever use of oral contraceptive (n=8,426; 2.6%), infertility problems (n=110,350; 34.6%)
P-values were from t-test, Wilcoxon test, or chi-square test as appropriate

Table 3. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of differentiated thyroid cancer according to 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)

C=Component

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

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

Table 4. Hazard ratios (HRs) and 95% confidence intervals (CIs) of the risk of differentiated thyroid cancer according to 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)

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

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

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