Inflammatory potential of the diet and association with risk of differentiated thyroid cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort

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Abbreviations:

BMI: body mass index; CI: confidence interval; CRP: C-reactive protein; DII: dietary inflammatory index; DTC: differentiated thyroid cancer; E-DII_d: dietary inflammatory index adjusted on energy intakes using the density method; E-DII_r: dietary inflammatory index adjusted on energy intakes using the residual method; EPIC: European Prospective Investigation into Cancer and Nutrition; FFQ: food frequency questionnaire; HR: hazard ratio; IARC: International Agency for Research on Cancer; IL: interleukin; ISD: Inflammatory Score of the Diet; SD: standard deviation; TNF: tumor necrosis factor

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Abstract:

Purpose: Chronic inflammation is thought to initiate or promote differentiated thyroid cancer (DTC) and previous studies have shown that diet can modulate this inflammatory process. We aimed to evaluate the association of several dietary scores reflecting the inflammatory potential of the diet with DTC risk.

Methods: Within the EPIC cohort, 450 063 participants were followed for 14 years, and 712 newly incident DTC cases were identified. Associations between four dietary inflammatory scores [the dietary inflammatory index (DII®) and two energy-adjusted derivatives (the E-DII$_r$ and the E-DII$_d$), and the Inflammatory Score of the Diet (ISD)] and DTC risk were evaluated in the EPIC cohort using multivariable Cox regression models.

Results: Positive associations were observed between DTC risk and the DIIs (HR for 1 SD increase in DII: 1.11, 95%CI: 1.01, 1.23, similar results for its derivatives), but not with the ISD (HR for 1 SD increase: 1.04, 95%CI: 0.93, 1.16).

Conclusion: Diet-associated inflammation, as estimated by the DII and its derivatives, was weakly positively associated with DTC risk in a European adult population. These results suggesting that diet-associated inflammation acts in the etiology of DTC need to be validated in independent studies.

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Conflicts of Interest: Dr. Marie-Christine Boutron-Ruault declares two sponsored conferences outside the present work as: MAYOLI-SPINDLER: 03/07/2020 - 30/07/2020 Symposium: Pancreatology in practice in 2020 e-JFHOD 2020 Conference « Why do I see more and more pancreatic cancers? » GILEAD 04/12/2020 - 04/12/2020- e-conference Weight gain and HIV infection in 2020. Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company that has licensed the right to his invention of the dietary inflammatory index (DII®) from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. Dr. Nitin Shivappa is an employee of CHI. The subject matter of this paper will not have any direct bearing on that work, nor has that activity exerted any influence on this project.

Data Availability: EPIC data and biospecimens are available for investigators who seek to answer important questions on health and disease in the context of research projects that are consistent with the legal and ethical standard practices of IARC/WHO and the EPIC Centers. The primary responsibility for accessing the data obtained in the frame of the present publication belongs to the EPIC centers that provided them. The use of a random sample of anonymized data from the EPIC study can be requested by contacting epic@iarc.fr. The request will then be passed on to members of the EPIC Steering Committee for deliberation.

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.

Ethics approval: The study was conducted according to the guidelines of the Declaration of Helsinki. Approval for the EPIC study was obtained from the ethical review boards of the International Agency for Research on Cancer (IARC) and all national recruitment institutions. Informed consent was obtained from all EPIC participants.

Author contributions: The author's contribution were as follow – MCBR and TT coordinated the project. LL, NL, LD, SR, MCBR and TT designed and conducted the research; NS and JRH designed the DII; AA designed the ISD; LL performed the statistical analyses; NL, MCBR and TT supervised the statistical analyses; LL, NS, MCBR and TT interpreted the results and drafted the manuscript. All authors reviewed the manuscript and approved the final version of the paper.

INTRODUCTION

Thyroid cancer is the most common endocrine cancer, representing 3% of all cancers worldwide in 2018 [1]. Papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) are the most frequent subtypes of differentiated cancer (DTC), representing about 90% of all thyroid cancers. DTC is more frequent in women and its incidence has been continuously increasing over the last three decades, particularly in high-income countries [2]. Increased incidence is mostly attributable to overdiagnosis [3] but also to changes in environmental and lifestyle exposures [4]. To date, only a few risk factors have been well-established including a history of benign thyroid diseases, exposure to ionizing radiations during childhood, and high body mass index [5, 6]. In women, some reproductive and menstrual factors have been associated with an increase risk of thyroid cancer [7]. Several dietary factors, such as total energy intake [8], flavanones [9], and nitrites [10] have been positively associated with thyroid cancer risk, while high intakes of iodine (depending on the type of thyroid cancer) [11], polyunsaturated fatty acids [8], cruciferous vegetables [12], alcohol [13], and flavan-3-ols [9] have been inversely associated with thyroid cancer risk. However, associations with these factors are not consistent in the literature making the epidemiological evidence still inconclusive. Therefore, the role of dietary factors in thyroid carcinogenesis is still not clearly understood.

Evidence suggests that chronic, systemic low-grade inflammation initiates or promotes carcinogenesis [14]. Although causal agents and mechanisms have been proposed for several cancers such as gastric, lung, prostate, or colorectal cancer [15, 16], the role of inflammation in the development of thyroid cancer appears particularly complex and is not well understood. Thyroid autoimmune diseases and above all, obesity, both being chronic systemic inflammatory conditions, have been previously associated with thyroid cancer risk [17, 18]. Previous studies showed positive associations between inflammatory biomarkers and DTC

risk[19]. In the EPIC study, DTC risk was positively associated with interleukin (IL)-10 and inversely associated with adiponectin [20].

Several single dietary factors, such as flavonoids, glycemic index, fiber, saturated fatty acids or Mediterranean diet, have been shown to have an impact on blood concentrations of inflammatory markers, including cytokines, chemokines, acute-phase proteins, soluble adhesion molecules, and cytokine receptors [21, 22]. However, tools such as dietary scores or patterns are needed to consider potential synergistic or antagonist effects, and to measure the dietary inflammation load of the whole diet rather than single dietary factors. During the last two decades, various scores have been developed to investigate the contribution of the whole diet to inflammatory processes [23–26]. Only two case-control studies [27, 28] have investigated the association between such scores and thyroid cancer risk, and reported a positive association between a pro-inflammatory diet and the risk of DTC. The aim of the present study was to investigate, for the first time prospectively, the relationship between dietary inflammatory scores and DTC risk, in the large EPIC cohort.

MATERIALS AND METHODS

Study population

The EPIC cohort is a multicenter prospective study including 521 323 men and women from 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and United Kingdom). The study was designed to investigate the associations between nutritional, lifestyle, metabolic, and genetic risk factors, and cancer risk. Participants were enrolled between 1992 and 1998, mostly aged 30-70 y, from the general population. Characteristics of the study population and baseline data collection methods have been described previously [29]. All participants gave written informed consents, and the study was approved by the Ethics Review Committee of the International Agency for Research on Cancer (IARC) and by the local ethical committees of the individual EPIC centers.

Prior to analysis, the following exclusions were made: participants with a prevalent cancer at baseline (n=25 184), those with missing follow-up information (n=4 148), those from Greece due to data restriction issues (n=26 916), those with a non-differentiated thyroid cancer subtype (n=48), those with missing dietary information (n=5 900), and those in the highest or lowest 1% of the distribution for the ratio of energy intake to estimated energy requirement (n=9 064). Therefore, our final study population included 450 063 participants (131 416 men and 318 647 women, see flowchart in **Supplementary Figure S1**).

Follow-up and ascertainment of differentiated thyroid cancer

Incident cancer cases were identified through record linkage with population cancer registries in most countries. In France and Germany, a combination of methods was used including health insurance records, cancer and pathology registries, and active follow-up of study participants. Data on vital status were obtained from mortality registries at the regional or national level. Closure dates of the study period were defined as the latest dates of complete follow-up for both cancer incidence and vital status. During follow-up, a total of 812 cases were defined as newly diagnosed with a first primary thyroid cancer (code C73 according to the International Classification of Diseases, 10th Revision). Among them, 48 participants with non-differentiated thyroid cancer (e.g., anaplastic, medullary, lymphoma, or "other morphologies") were excluded, as well as 52 participants due to the exclusion criteria mentioned in the above section (see flowchart in **Supplementary Figure S1**). Thus, a total of 712 incident DTC cases were included (573 papillary, 108 follicular, and 31 not otherwise specified, which are likely to be papillary).

Data collection and dietary assessment

Lifestyle questionnaires were used to collect data on sociodemographic characteristics, tobacco smoking, physical activity, education, medical history, and reproductive history [29].

Anthropometric data were measured, except in EPIC-Oxford, Norway, and France, where they were self-reported [30]. About 386 000 participants also provided a blood sample at recruitment.

The usual diet over the previous year was assessed at baseline using a validated country/center-specific dietary questionnaire [29, 31]. In most countries, extensive quantitative food frequency questionnaires (FFQs) or semi quantitative FFQs were used, though some used diet history questionnaires or a combination of dietary records and FFQs. The standardized EPIC Nutrient Database was used to estimate total energy and nutrient intakes [32].

Dietary inflammatory scores computation

In the present study, four dietary inflammatory scores reflecting inflammatory potential of the diet were computed: the dietary inflammatory index (DII®) [24], the dietary inflammatory index adjusted on energy intake using the residual method (E-DII$_r$), the dietary inflammatory index adjusted on energy intake using the density method (E-DII$_d$), and the Inflammatory Score of the Diet (ISD) [26].

To compute these scores, literature-derived coefficients were assigned to every micronutrient, macronutrient, or food parameter associated with an increase (+1), a decrease (−1), or no effect (0) on six of the following inflammatory biomarkers: IL-1β, IL-4, IL-6, IL-10, tumor necrosis factor (TNF)-α, and CRP, based on a detailed literature review [24]. These coefficients were weighted based on study design and were called inflammatory effect scores. Depending on the scores, from 28 to 32 food parameters were included for this study. The intakes of the food parameters were standardized, then expressed as cumulative proportions (with values ranging from zero to one), and then centered on zero by doubling the proportion and subtracting one. Finally, these values were multiplied by their respective inflammatory

effect scores and summed across all food parameters to obtain the dietary inflammation scores, with higher scores reflecting a more pro-inflammatory diet. The four scores differed in the manner in which total energy intake was considered, the reference population used to standardize the dietary intakes, and the food parameters included. The list of these parameters and the methods used for calculating the dietary inflammatory scores are summarized in **Supplementary Table S1**.

The DII and its variants are based on a wide expanse of the literature that takes into account nearly 2000 studies in humans, laboratory animals, and cell culture experiments rather than on a single study, dietary recommendation, or cuisine or foodway. Therefore, the DII has the ability to adapt to various populations across the globe. A complete description of the DII calculation is available elsewhere [24]. To avoid the arbitrariness resulting from simply using raw consumption amounts, intakes of food parameters were then standardized to a representative range of dietary intakes based on actual human consumption in 11 populations living in different countries across the world that provided an estimate of a mean and standard deviation for each parameter.

A complete description of the ISD calculation is available elsewhere [26]. Its computation is very similar to the DII, however, there are slight differences. First, intakes of food parameters were standardized with the use of the mean and SD of the EPIC population (instead of the 11 countries). Second, total fat is not included in the food parameters to avoid including its inflammatory effect in duplicate because saturated, monounsaturated, and polyunsaturated fats are already included. Finally, because the negative relation between alcohol and inflammatory markers has been shown only among moderate consumers (<30–40 g/d) [33, 34], the weight for ethanol was set to 0 for participants with intake>40 g/d.

For the DII and the ISD, no adjustment on energy intake was performed. For the E-DIIr, the food intakes were adjusted on energy intake using the residual method [35] while for the E-

DIId, these reported amounts were converted to an amount per 1000kcal of energy intake. Computing E-DIIr and E-DIId required using an energy-adjusted version of this global comparative database.

Statistical analysis

First, descriptive analyses were carried out. The means (SD) of the four scores adjusted for sex and age at baseline (and for alcohol-free energy intake for the ISD and the DII) were presented according to the main characteristics of the study population.

Second, to assess the prospective association between DTC risk and the inflammatory potential of the diet measured by the dietary inflammatory scores, HRs (Hazard Ratios) and 95% CIs (Confidence Intervals) were estimated using Cox proportional hazards models with age as the time scale. Participants were followed from age at baseline until age at diagnosis of DTC, at death, at last follow-up, or at the end of the follow-up period, whichever occurred first.

Dietary inflammatory scores were modelled in two ways. First, they were fit as a continuous variable and estimates were reported for a 1-SD increase assuming linear associations. Second, dietary inflammatory scores were categorized into sex-and-country-specific quartile groups and the first quartile group was considered as the reference category. Tests for trend across quartiles were conducted by fitting models using a quantitative variable equal to the median value of the exposure classes.

All Cox models were stratified by year of birth (5-y classes) to take into account the cohort effect, and by sex and center, and adjusted for age (timescale). Furthermore, the multivariable models were additionally adjusted for the following potential confounders selected *a priori*: BMI (continuous), smoking status (never smokers or not specified, former smokers, current smokers), education (none or primary school completed / technical, professional school or

148 secondary school / longer education / not specified), and physical activity (inactive,
149 moderately inactive or not specified / active or moderately active according to the Cambridge
150 physical activity index). Multivariable models were further adjusted for alcohol-free energy
151 intake for the DII and the ISD because computation of those scores did not consider energy.
152 Analyses also were restricted to women and were additionally adjusted for histories of
153 ovariectomy and hysterectomy. We did not conduct separate analyses for men as the sample
154 size was too small for meaningful analyses.

155 Possible interactions between the scores, and BMI and the smoking status on the risk of DTC
156 were examined using the likelihood ratio test comparing models with and without the
157 interaction term in the Cox model. Separate models were defined to assess the risk of DTC by
158 subtype (papillary and follicular) and by country. The heterogeneity of HRs across DTC
159 subtypes and across countries was explored using a meta-analytic random effects model.
160 Finally, a sensitivity analysis was conducted to evaluate possible reverse causality by
161 excluding subjects with ≤2 y of follow-up.

162 Statistical analyses were performed using SAS Enterprise Guide software (v7.1, Cary, NC,
163 USA) and all tests were two-sided.

164 RESULTS

165 During a mean follow-up of 14 years, 712 (90% women) first incident DTC cases were
166 identified, including 573 papillary and 108 follicular tumors, among the 450,063 participants
167 included in the present study. The average age and BMI of the participants were 51 and 25
168 respectively. They were mostly non-smokers (never and former, 78%). Distributions of the
169 ISD, the DII, the E-DII$_d$ and the E-DII$_r$ in the whole cohort are shown in **Supplementary**
170 **Table S1** and in **Supplementary Figure S2**. The DII was strongly correlated with the ISD
171 and the E-DII$_r$ (Pearson coefficients>0.9), and to a lesser extent with the E-DII$_d$ (Pearson

coefficient=0.62). The E-DII$_r$ was also strongly correlated with the ISD and the E-DII$_d$ (Pearson coefficient>0.75), and the Pearson coefficient of correlation between the ISD and the E-DII$_d$ was 0.50 (see **Supplementary Table S2**). The means of the four scores adjusted for sex and age at baseline (and for alcohol-free energy intake for the ISD and the DII) according to the main characteristics of the population are presented in **Table 1**. Incident DTC cases, participants from Italy, The Netherlands, Germany, and Sweden, smokers, and excess weight participants (BMI≥ 25) had a more pro-inflammatory diet, while participants from the United Kingdom had a more anti-inflammatory diet. The four scores decreased as education level or physical activity increased. Percentages of variation of means of daily intake of selected nutrients and food groups between the lowest and highest sex- and country-specific quartiles of dietary inflammatory scores [(Quartile 4-Quartile1)/Quartile 1)*100] are presented in **Supplementary Table S3**. Carbohydrates and proteins had negative percentages of variation according to the ISD, the DII and the E-DII$_r$, while it was positive according to the E-DII$_d$. Ethanol had positive percentages of variation according to the ISD and the E-DII$_d$, while it was negative according to the DII and E-DII$_r$. Total fat had positive percentages of variation according to all scores except for the E-DII$_r$. Positive percentages of variation were also observed for saturated fat and cholesterol, while negative percentages of variation were observed for fiber, β-carotene, thiamin, vitamins B6, B9, C, D, and E, iron, and magnesium. In terms of food groups, potatoes and other tubers, vegetables, legumes, fruit, cereals, fish, and non-alcoholic beverages had negative percentages of variation according to all scores, except for the E-DII$_d$ for potatoes and other tubers, and cereals, while dairy products, meat, fat, sugar and confectionary, and cakes and biscuits had positive percentages of variation according to all scores, except for the E-DII$_r$ for fat. Alcoholic beverages had positive percentages of variation according to the ISD and the E-DII$_d$, while they were negative according to the DII and E-DII$_r$.

Associations of the dietary inflammatory scores with DTC risk in the EPIC cohort are presented in **Table 2**. The three DIIs were positively associated with DTC risk, and no association was found for the ISD. In the multivariable model, the risk of DTC increased by 11% for each 1-SD increase in the DII (HR: 1.11; 95% CI: 1.01, 1.23). We reported a 24% increased risk of DTC comparing the highest *vs*. lowest quartile of E-DII$_r$ (HR: 1.24; 95% CI: 1.00, 1.53). When analyses were restricted to women, similar results were observed (**Supplementary Table S4**). Associations between the dietary inflammatory scores and DTC risk by country are presented in **Figure 1**, and we observed no significant heterogeneity between countries. Finally, excluding participants with ≤2 y of follow-up led to results similar to those based on the whole cohort, and positive but not statistically significant associations between the dietary inflammatory scores and the risks of papillary DTC and follicular DTC, individually, were observed (see **Supplementary Table S5**).

Because smoking and BMI are known to contribute to low-grade chronic inflammation, we also explored the interaction between these factors and the dietary inflammatory scores on DTC risk (see **Supplementary Table S6**). Although the associations between the scores and DTC seemed to be higher for participants with excess weight (e.g., HR for 1-SD increase in the E-DII$_d$: 1.03; 95% CI: 0.91, 1.16 in participants with BMI <25 kg/m^2 *vs.* 1.16; 95% CI: 1.02, 1.32 in participants with BMI ≥25 kg/m^2), the interaction term was not statistically significant. No interaction was found with the smoking status.

DISCUSSION

In the present study, we showed a positive, but weak, association between the three DIIs and DTC risk in a population of European adults. Each increase of 1 SD of the DIIs increased the DTC risk by 8% to 11%; and participants having a diet categorized in the highest quartiles of dietary inflammatory scores had an 18% to 25% increased DTC risk compared with those in

the lowest quartiles. Associations were more pronounced among participants with higher BMIs.

DIIs and ISD differed in the reference population used to standardize the dietary intake: the ISD was based on the EPIC population while the DIIs used a worldwide database of 11 countries. These scores also differed in the way energy was taken into account: the DII and ISD considered energy as an inflammatory parameter because energy can act in itself as a pro-inflammatory factor through the increase in adipose tissue [36], while the E-DIIs did not consider energy as an inflammatory parameter in the calculation of the score, but used standardized energy-adjusted intakes [37]. Worthy of note is the importance of controlling for energy intake in the development of such dietary indices [35]. Indeed, subjects with higher overall food consumption tend to have higher intakes in all micronutrients –therefore higher dietary scores – but also higher energy intakes [36]. Moreover, total fat is not included in the ISD to avoid including its inflammatory effect in duplicate (saturated, monounsaturated, and polyunsaturated fats are already included). On another note, the weight for ethanol was set to 0 for participants with intakes>40 g/d in the ISD because the negative relation between alcohol and inflammatory markers has been shown only among moderate consumers (<30–40 g/d) [33, 34], while it was set to –0·278 in the DIIs regardless of the amount consumed. Finally, DIIs include more anti-inflammatory parameters (such as caffeine, garlic and tea) than the ISD, which could be important drivers of the DIIs scores and could allow a better estimate of the inflammatory potential of the diet. All these differences, and particularly in the reference population used and in the ethanol weight (given the inverse association between alcohol and DTC risk [38]), could explain the difference in the associations observed between the DIIs and the ISD.

To our knowledge, our study is the first study to prospectively investigate the relationship between dietary inflammatory scores and DTC risk. Two case-control studies on DTC from the EPITHYR consortium previously reported a positive association between the dietary inflammatory scores and DTC risk in a population from New Caledonia [27] and from metropolitan France [28]. Both studies observed a more striking association in ever smokers and overweight individuals, two inflammatory conditions. Regarding other cancers, numerous positive associations with dietary inflammatory scores have been published in the literature, as for instance with colorectal, breast, and prostate cancer risks [39]. In particular, a recent study within the EPIC cohort showed a positive association between the ISD and breast cancer risk, with a stronger association among premenopausal women [40].

In our study, individuals in the highest quartile of dietary inflammatory scores have a higher consumption of bakery/sugar items, meat and dairy intakes but a lower consumption of vegetables, fish and shellfish, legumes, and fruits than individuals in the lowest quartile of dietary inflammatory scores (Supplementary Table S3). The positive association we reported between DTC risk and inflammatory score is partly in accordance with previous studies based on food groups. In the EPIC cohort, the associations between DTC and intakes of fruits and vegetables [41] or fish [42] were not significant while a meta-analysis of 19 case-control studies reported a weak inverse association with intake of vegetables, no association with intake of fruits and a negative association with fish and shellfish intake but only in iodine deficiency areas [43]. The other food groups were only little studied in association with DTC.

As a pro-inflammatory diet was associated with an increased risk of DTC in our study, we can hypothesize that diet acts on the etiology of DTC through inflammatory pathways. A previous analysis on circulating levels of inflammatory biomarkers and DTC risk conducted in a nested case-control study within the EPIC cohort showed a positive association with IL-10 and a negative association with adiponectin, while no association was found with leptin, CRP, IL-6,

and TNF-α [20]. We conducted supplementary analyses in this nested case-control study to investigate whether the association between the dietary inflammatory scores and DTC risk could be mediated by inflammatory biomarkers. We found positive associations between the dietary inflammatory scores and levels of C-reactive protein (CRP) and IL-6 in the controls (see **Supplementary Table S7**), but no association between the scores and DTC risk was observed in the nested case-control subset, probably due to lack of statistical power when the analysis is restricted to this subsample (see **Supplementary Table S8**). Therefore, we were not able to further investigate the mediating role of inflammatory biomarkers. However, two major inflammatory processes support the role of inflammation in DTC etiology: a perturbation of the microenvironment via infiltration of the tumor by inflammatory cells, cytokines, or chemokines, and the activation of oncoprotein-mediated signaling present in epithelial cancer cells [44]. Moreover, we reported a stronger association between the inflammatory potential of the diet and DTC risk in individuals with excess weight, which might be explained by an enhanced release of pro-inflammatory cytokines by the adipose tissue [45].

Major strengths of our study were the prospective design with a long follow up and a large sample size with a relatively high number of DTC cases. Moreover, we implemented a macroscopic approach to assess diet-related inflammation using multiple dietary inflammatory scores. Some study limitations also need to be considered. First, as information on the usual diet was self-reported, we cannot rule out cognitive limitations and social desirability bias. However, we used validated tools [46] and a validated country/center-specific dietary questionnaire [29, 31]. Furthermore, subjects with extreme energy intake were excluded to minimize the potential for measurement error in the usual diet, and due to the prospective design, any misclassification of exposure is likely to be non-differential with respect to disease status and would result in an attenuation of the associations (i.e., bias

towards the null). Second, dietary intakes were established at enrolment and several years have passed before cancer diagnosis. Changes in dietary habits over time may have occurred and this could explain the fact that the association between the inflammatory potential of the diet and DTC risk appeared stronger in previously published case-control studies [27, 28] than in the present prospective study. Furthermore, the original questionnaires were not designed to measure inflammatory diets, hence the countries varied in which elements of the scores they have included in their questionnaires. This means that country-specific results must be interpreted with caution. Finally, although we controlled for several confounding factors, we cannot exclude the possibility that residual confounders also may have influenced our observations.

To conclude, our study showed a weak positive association between dietary inflammatory indexes and DTC risk in a population of European adults. These results suggest that diet acts on the etiology of DTC through inflammatory reactions, but they need to be replicated in other independent studies, and the mediating role of inflammatory biomarkers needs to be further investigated. In such studies, great care will need to be taken in establishing temporal/sequence of events. Additionally, experimental studies need to be designed and conducted so as to deepen our understanding of mechanisms linking inflammation to DTC. Furthermore, with regard to public health implications, these dietary inflammatory scores are complex constructs which are difficult to be translated in recommendations. However, our findings support the strategy of consuming a diet rich in anti-inflammatory elements, with ample amounts of vegetables for instance, to limit the inflammatory potential of the diet and prevent DTC.

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Table 1. Mean of the dietary inflammatory scores adjusted for sex and age at baseline according to the main characteristics of the population (N=450 063)

	ISD Mean[1] (SD)	DII Mean[1] (SD)	E-DII$_d$ Mean[2] (SD)	E-DII$_r$ Mean[2] (SD)
DTC status at the end of follow-up				
No	0.592 (0.002)	0.816 (0.003)	1.159 (0.003)	0.150 (0.003)
Yes	0.798 (0.055)	1.081 (0.064)	1.526 (0.061)	0.383 (0.064)
Country				
France	0.547 (0.005)	0.408 (0.006)	1.296 (0.006)	-0.294 (0.006)
Italy	1.470 (0.006)	1.902 (0.007)	2.468 (0.007)	1.198 (0.007)
Spain	0.585 (0.006)	0.295 (0.007)	0.571 (0.007)	-0.370 (0.007)
United Kingdom	-0.999 (0.005)	-0.713 (0.005)	-0.309 (0.005)	-1.389 (0.005)
The Netherlands	0.910 (0.007)	1.270 (0.008)	1.409 (0.008)	0.601 (0.008)
Germany	0.912 (0.006)	1.749 (0.007)	1.695 (0.006)	1.127 (0.007)
Sweden	1.415 (0.006)	1.836 (0.007)	1.917 (0.006)	1.119 (0.007)
Denmark	0.499 (0.005)	0.517 (0.006)	1.159 (0.006)	-0.102 (0.006)
Norway	1.265 (0.007)	0.990 (0.008)	0.775 (0.008)	0.336 (0.008)
Education				
None / Primary school completed	0.988 (0.004)	1.190 (0.005)	1.417 (0.005)	0.513 (0.005)
Technical/professional school / Secondary school	0.633 (0.003)	0.872 (0.004)	1.203 (0.004)	0.206 (0.004)
Longer education (incl. University deg.)	0.225 (0.004)	0.431 (0.005)	0.923 (0.005)	-0.221 (0.005)
Not specified / Missing	-0.553 (0.011)	-0.176 (0.013)	0.194 (0.013)	-0.875 (0.013)
Smoking status				
Never / Not specified	0.486 (0.003)	0.74 (0.004)	1.098 (0.004)	0.049 (0.004)
Former	0.428 (0.004)	0.642 (0.005)	0.983 (0.005)	-0.012 (0.005)
Smoker	0.996 (0.005)	1.178 (0.005)	1.498 (0.005)	0.542 (0.005)
Physical activity				
Inactive / Moderately inactive	0.654 (0.003)	0.895 (0.004)	1.228 (0.004)	0.227 (0.004)
Active / Moderately active	0.520 (0.003)	0.726 (0.004)	1.081 (0.004)	0.062 (0.004)
BMI (kg/m²)				
< 25	0.529 (0.003)	0.745 (0.004)	1.162 (0.004)	0.075 (0.004)
≥ 25	0.652 (0.003)	0.885 (0.004)	1.157 (0.004)	0.221 (0.004)

BMI: Body Mass Index; DTC: Differentiated Thyroid Cancer; SD: Standard Deviation

[1] Adjusted for sex, age at baseline and alcohol-free energy intake

[2] Adjusted for sex and age at baseline

Table 2. Hazard Ratios (95%CIs) of thyroid cancer according to the dietary inflammatory scores in the EPIC study

		n (%)	DTC (%)	Model 1			Model 2		
				HR	95%CI	P	HR	95%CI	*P*
ISD[a]									
	For 1-SD increase	450063	712	1.02	(0.93,1.11)	0.71	1.04	(0.93,1.16)	0.48
	Quartiles groups					0.56			0.36
	Q1	112509 (25.00)	180 (25.28)	1	Reference		1	Reference	
	Q2	112519 (25.00)	177 (24.86)	1.00	(0.81,1.23)		1.02	(0.83,1.27)	
	Q3	112523 (25.00)	173 (24.30)	0.99	(0.80,1.22)		1.03	(0.82,1.30)	
	Q4	112512 (25.00)	182 (25.56)	1.07	(0.87,1.32)		1.14	(0.88,1.47)	
DII[a]									
	For 1-SD increase	450063	712	1.08	(0.99,1.18)	0.09	1.11	(1.01,1.23)	0.04
	Quartiles groups					0.10			0.05
	Q1	112509 (25.00)	170 (23.88)	1	Reference		1	Reference	
	Q2	112519 (25.00)	171 (24.02)	1.00	(0.81,1.24)		1.02	(0.82,1.26)	
	Q3	112523 (25.00)	177 (24.86)	1.05	(0.85,1.30)		1.09	(0.87,1.36)	
	Q4	112512 (25.00)	194 (27.25)	1.18	(0.95,1.45)		1.25	(0.99,1.57)	
E-DII$_d$									
	For 1-SD increase	450063	712	1.08	(0.99,1.18)	0.08	1.08	(0.99,1.19)	0.07
	Quartiles groups					0.06			0.06
	Q1	112509 (25.00)	170 (23.88)	1	Reference		1	Reference	
	Q2	112519 (25.00)	157 (22.05)	0.89	(0.72,1.11)		0.89	(0.72,1.11)	
	Q3	112523 (25.00)	182 (25.56)	1.03	(0.84,1.27)		1.04	(0.84,1.28)	
	Q4	112512 (25.00)	203 (28.51)	1.17	(0.95,1.44)		1.18	(0.95,1.45)	
E-DII$_r$									
	For 1-SD increase	450063	712	1.09	(0.99,1.19)	0.07	1.09	(0.99,1.19)	0.08
	Quartiles groups					0.04			0.05
	Q1	112509 (25.00)	159 (22.33)	1	Reference		1	Reference	
	Q2	112519 (25.00)	177 (24.86)	1.09	(0.88,1.35)		1.09	(0.88,1.35)	
	Q3	112525 (25.00)	178 (25.00)	1.10	(0.89,1.37)		1.10	(0.88,1.36)	
	Q4	112510 (25.00)	198 (27.81)	1.25	(1.01,1.54)		1.24	(1.00,1.53)	

CI: Confidence Interval; DTC: Differentiated Thyroid Cancer; EPIC: European Prospective Investigation into Cancer and Nutrition; HR: Hazard Ratio; SD: Standard Deviation

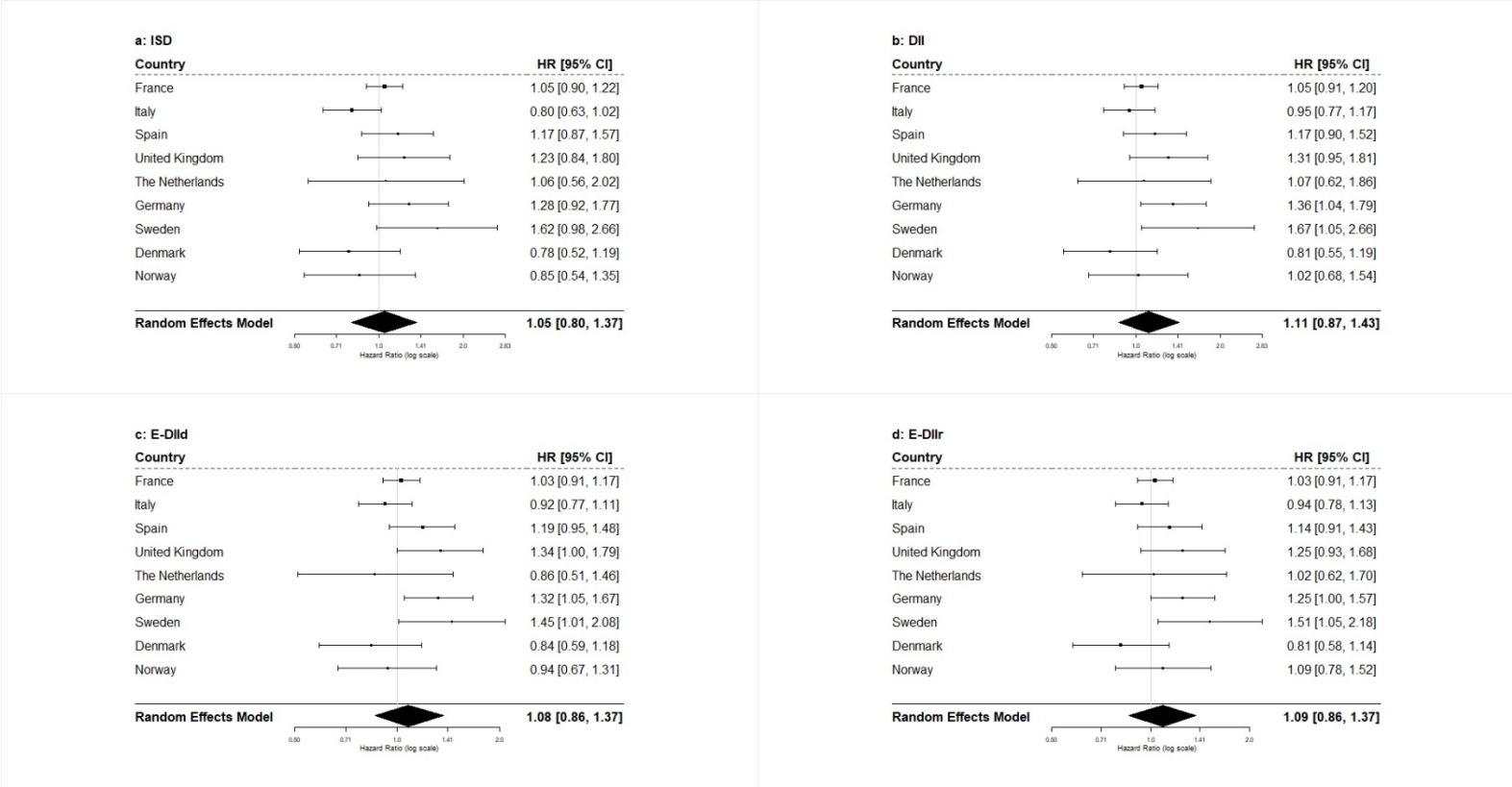
Model 1: adjusted for age (as timescale) and stratified by year of birth, sex and center

Model 2: further adjusted for BMI, education, smoking and physical activity

[a] Further adjusted for alcohol-free energy intake

Figure 1. Associations between the dietary inflammatory scores and thyroid cancer risk in EPIC by country.

HR (95% CI) for each 1 SD increase of the dietary inflammatory scores, estimated from a Cox model stratified by year of birth, sex and center and adjusted for age (as timescale), BMI, education, smoking, and physical activity. Models for the ISD and the DII were further adjusted on alcohol-free energy intake. Heterogeneity test: $Q_{(8\ df)} = 2.36$ (*P*: 0.97), 1.99 (*P*: 0.98), 2.19 (*P*: 0.97) and 1.69 (*P*: 0.99) for the ISD, the DII, the E-DII_d and the E-DII_r, respectively.



Supplementary Materials