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# Adherence to mediterranean diet and the risk of differentiated thyroid cancer in a European cohort: The EPIC study

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**Background:** The Mediterranean diet (MD) has been proposed as a healthy diet with a potential to lower the incidence of several types of cancer, but there is no data regarding thyroid cancer (TC). We investigated the association between MD adherence, and its components, and the differentiated TC risk within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.

**Methods:** Over 450,000 men and women from nine European countries were followed up for a mean of 14.1 years, during which 712 differentiated TC cases were identified. Adherence to MD was estimated using the relative MD (rMED) score, an 18-point scale including alcohol, and the adapted rMED (arMED) score, a 16-point scale excluding alcohol. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox regression models adjusted for potential confounding factors.

**Results:** Adherence to the arMED score was not associated with the risk of differentiated TC ( $HR_{\text{high vs. low adherence}} = 0.94$ , 95% CI: 0.70–1.25;  $p$ -trend 0.27), while a suggestive, but non-statistically significant inverse relationship was observed with rMED ( $HR_{\text{high vs. low adherence}} = 0.88$ , 95% CI: 0.68–1.14;  $p$ -trend 0.17). Low meat ( $HR_{\text{low vs. high meat intake}} = 0.81$ , 95% CI: 0.67–0.99;  $p$ -trend = 0.04) and moderate alcohol ( $HR_{\text{moderate vs. non-moderate intake}} = 0.88$ , 95% CI: 0.75–1.03) intake were related with lower differentiated TC risk.

**Conclusions:** Our study shows that a high adherence to MD is not strongly related to differentiated TC risk, although further research is required to confirm the impact of MD and, especially, meat intake in TC risk.

#### KEYWORDS

thyroid cancer (TC), Mediterranean diet (MD), meat, intake, EPIC study, cohort

## Introduction

Thyroid cancer (TC) represents the most common endocrine malignancy worldwide (1). Lastly, the TC incidence has gradually increased, in part driven by overdiagnosis due to the use of ultrasound examinations and increased medical surveillance, leading to higher TC prevalence in high-income countries (2). The transformation of thyroid follicular cells may result in differentiated or undifferentiated TC. Differentiated TC, including papillary and follicular carcinoma, represents more than 90% of all TC cases (3). Poorly differentiated and anaplastic thyroid carcinomas are rare but more aggressive tumor types (3). Exposure to ionizing radiation, particularly during childhood (4), previous history of benign thyroid hyperplasia (5), and

overweight/obesity (6, 7) are the mostwell-established risk factors for TC.

The Mediterranean diet (MD) is characterized by a high consumption of fruits, vegetables, complex carbohydrates and fish, a low amount of meat and dairy products and a daily glass of wine (8). In this dietary pattern, olive oil is the main source of fats (9). There is evidence that relates high adherence to MD with lower risk of cancer incidence and mortality (e.g., breast, colorectal, head and neck, respiratory, gastric, liver and bladder) (10, 11), obesity (12), and type 2 diabetes (13). Convincing evidence is consistently showing a positive moderate association for overweight and obesity (6, 7), and type 2 diabetes (14, 15) with TC incidence. MD is rich in polyphenols, fibers, phytosterols, monounsaturated and polyunsaturated fatty acids, which are probably the main drivers of the protection of MD against cancer (16). The potential underlying mechanisms of action involve anti-oxidative and anti-inflammatory effects, reduction of tumor cell growth, increase of chemoprotective effects, and inhibition of tumor development (16). Several dietary factors of MD have been suggested to play a role in TC etiology, but the results are inconclusive (17, 18). Previous

Abbreviations: arMED, adapted relative Mediterranean diet score; BMI, body mass index; EPIC, European Prospective Investigation into Cancer and Nutrition; MD, Mediterranean diet; rMED, relative Mediterranean diet score; TC thyroid cancer; T3 triiodothyronine; T4 thyroxine.

studies investigating TC have mainly focused on separate food items and only few on dietary patterns (17, 18). Dietary pattern analysis examines the overall effects of diet and could be a better approach to investigate the role of diet in chronic diseases (19).

To our knowledge, there are no studies on the relationship between MD adherence and TC risk. Therefore, in the current study we aimed to investigate the association between MD adherence and the risk of differentiated TC within the European Prospective Investigation into Cancer and Nutrition (EPIC) study.

## Materials and methods

### Subjects and study design

EPIC is a large prospective cohort study designed to investigate the relationship between diet, lifestyle, environmental factors, and cancer. The full methods and study design have been described previously (20). In brief, 521,324 participants, mostly aged between 35 and 70 years, were recruited between 1992 and 2000 in 23 centers from 10 Western European countries. All participants provided written informed consent, and the study was approved by the local ethics committees in the participating countries and the ethical review board of the International Agency for Research on Cancer (IARC). We excluded participants with prevalent cancer other than non-melanoma skin cancer at baseline or with missing information on date of diagnosis or censoring data, missing dietary and lifestyle information (did not complete the questionnaires), had extreme energy intake and/or expenditure (participants in the top or bottom 1% of the distribution of the ratio of total energy intake to energy requirement) and participants from Greece (data not provided for the current study) (Supplementary Figure 1).

### Dietary and lifestyle ascertainment

Dietary information was collected at enrollment, using country-specific dietary questionnaires (20). Total energy intake was estimated by using the standardized EPIC Nutrient Database (21). At baseline, information on socio-demographic characteristics, tobacco consumption, physical activity, reproductive history, use of oral contraceptives and hormone replacement therapy, and medical history were self-reported using standardized lifestyle questionnaires (20). Anthropometry (weight and height) was measured at recruitment by trained personnel, except for Oxford (United Kingdom), Norway, and France, where measurements were self-reported.

The adherence to MD was measured using the adapted relative MD score (arMED), a version of the relative MD (rMED) (22) based on the original MD score by Trichopoulou et al. (23), excluding alcohol. The arMED incorporates 8 selected

components of MD and is a 16-point scale. Each component was calculated as a function of energy density (g/2,000 kcal per day) and then divided into cohort-wide tertiles of intakes (except for olive oil). For five of the six components that positively reflect MD: fruits (including nuts and seeds), vegetables (excluding potatoes), legumes, fish (including seafood), and cereal products, a score of 0-1-2 was assigned to the lowest to highest intake tertiles, respectively. The score was inverted (2-1-0 assigned to the intake tertiles) for the two components that negatively reflect MD: total meat (red meat, processed meat, poultry, game, and offal) and dairy products. The score for olive oil was adapted for non-Mediterranean countries owing to their low consumption, by assigning 0 to non-consumers, 1 for subjects below the median intake and 2 for subjects equal to or above this median. The arMED score was further classified into low (0-5 points), medium (6-9 points) or high (10-16 points) adherence levels, as previously categorized in the EPIC study (10).

In a previous EPIC study, moderate alcohol intake was inversely associated with differentiated TC risk (24). Therefore, the rMED score (22), including alcohol, was also computed. The rMED incorporates the same previous 8 components plus alcohol and is an 18-point scale. Alcohol in the rMED score was scored dichotomously assigning 2 points for moderate consumption (sex-specific cut off points: 5-25 g per day for women and 10-50 g per day for men) and 0 points for intakes outside this range. The rMED score was further classified into low (0-6 points), medium (7-10 points) or high (11-18 points) adherence levels, as previously categorized in the EPIC study (22, 25).

### Follow-up and case assessment

Incident cancer cases were identified through population cancer registries in all countries except France Germany, and Naples (Italy) where cases were identified through active follow-up, directly from the participants and confirmed by a combination of methods, including health insurance records, and cancer and pathology registries. Vital status was obtained from mortality registries at the regional or national level. Complete follow-up censoring dates ranged from December 2010 to December 2014, depending on the study center. In this TC study (code C73 according to the International Classification of Diseases, 10th Revision), only first primary differentiated TC cases were included, and therefore, 52 undifferentiated TC (such as medullary, anaplastic, lymphoma, and other morphologies) were excluded (Supplementary Figure 1). Finally, 712 first primary incident differentiated TC cases were considered: 573 papillary TCs, 108 follicular TCs, and 31 not otherwise specified (NOS) TCs, most likely to be papillary TCs. Data on the stage of differentiated TC at diagnosis were collected from each center where possible. A total of 468 cases (65.7%) had tumor-node-metastasis staging score information, of which 371 were

TABLE 1 Description of the EPIC study by country and by adapted relative Mediterranean diet score (arMED).

Country	N	Women (%)	Differentiated thyroid cancer cases (n)				arMED score		arMED score (%)		
			Overall	Papillary	Follicular	NOS	Mean	SD	Low (0–5)	Medium (6–9)	High (10–16)
Denmark	55,005	52.2	39	28	11	0	6.0	2.5	44.5	46.4	9.1
France	67,391	100	248	227	19	2	8.9	2.4	7.5	51.7	40.8
Germany	48,551	56.4	82	58	21	3	6.6	2.2	31.6	58.2	10.2
Italy	44,543	68.5	127	97	19	11	10.4	2.1	0.9	33.9	65.2
Norway	33,972	100	36	31	4	1	7.8	2.1	13.6	65.8	20.6
Spain	39,984	62.1	80	66	13	1	10.7	2.2	1.3	26.2	72.5
Sweden	48,666	54.2	39	25	7	7	4.6	2.1	69.0	29.4	1.5
Netherlands	36,537	73.7	17	12	4	1	5.8	2.1	46.9	48.3	4.9
UK	75,415	69.7	44	29	10	5	8.7	2.4	10.1	51.6	38.2
Total	450,064	70.8	712	573	108	31	7.8	3.0	24.2	46.1	29.7

NOS: not otherwise specified; SD standard deviation.

classified as low-risk tumors (T1–T2) and 97 were classified as high-risk tumors (T3–T4).

## Statistical analysis

Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) between adherence to the MD measured by arMED and rMED score, its individual components and differentiated TC risk. Age was the primary time variable in all models. Entry time was age at recruitment and exit time was age at first diagnosis (cases), death, or censoring date (loss or end of follow-up), whichever occurred first. Both arMED and rMED scores were computed as categorical variables (low, medium, and high) and as continuous variables (per 1-unit). Trend tests were obtained by scoring the arMED or rMED categories in a continuous scale from 1 to 3. The basic model for the association between arMED and differentiated TC was stratified by sex, age at recruitment (1-year interval), study center, and adjusted for total energy intake (kcal/day). Variables associated with TC in previous EPIC studies (24, 26–28) were a-priori selected as potential confounders. Thus, the most-adjusted model was additionally adjusted for body mass index (BMI, kg/m<sup>2</sup>), smoking status, alcohol (g/day), education level and physical activity (according to the Cambridge Physical Activity Index) (29). In women the model was also adjusted for menopausal status and type, ever use of oral contraceptives, and history of infertility problems. Results from the two models were almost identical, therefore, the most-adjusted model was selected for presentation. Similar models were applied for the rMED score, without alcohol consumption (g/day) as adjustment variable. All models met the proportional hazard assumption, tested using the Schoenfeld goodness-of-fit test. In addition, we estimated the associations between individual components of MD and TC risk. Each component

was evaluated as a categorical variable (tertile points assigned for the arMED/rMED score calculation), except for alcohol (moderate vs. non-moderate consumption). Interactions on the multiplicative scale with sex, smoking status (never, former, and current smokers), alcohol (low, moderate, and high), BMI (<25 and ≥25 kg/m<sup>2</sup>), were examined using the likelihood ratio test.

Separate analyses were performed for differentiated TC subtypes: follicular and papillary tumors, and disease stage: low-risk (T1–T2) and high-risk (T3–T4) tumors. Heterogeneity of risk between TC subtypes was assessed with the Wald test. Separate models were also computed to check the variability between countries with a high and low TC incidence. EPIC countries with TC incidence rates of >5/10,000 in women (i.e., France, Germany, Italy, and Spain) were considered to have a high TC incidence. Moreover, separate models were conducted only in women, because of the small proportion of men with TC (10.4%). Finally, we conducted separate analyses by geographical regions: South (Spain, Italy, France), Central (UK, Germany, and the Netherlands) and North Europe (Denmark, Norway, and Sweden) because dietary habits can differ between European regions (30). Sensitivity analyses were performed by repeating the models after the exclusion of differentiated TC cases diagnosed during the first 2 years of follow-up, since participants may have changed their diets in the pre-diagnostic period. For all analyses, *p*-values < 0.05 were considered statistically significant. Statistical analyses were conducted using R 3.2.1 software.

## Results

In the current analysis of 450,064 EPIC participants (70.8% women), 712 were diagnosed with differentiated TC (89.6% women) (Supplementary Figure 1). The mean arMED score

TABLE 2 Baseline characteristics of included participants from the EPIC study according to the adapted relative Mediterranean diet score (arMED).

Characteristics	All	arMED score		
		Low (0-5)	Medium (6-9)	High (10-16)
<i>N</i>	450,064	108,791	207,470	133,803
<b>Sex, %</b>				
Women	70.8	53.6	74.7	78.9
Men	29.2	46.4	25.3	21.3
Age, years [mean (SD)]	51.1 (9.8)	51.9 (10.0)	51.5 (9.5)	49.9 (9.7)
Total energy, kcal/day [mean (SD)]	2,077 (619)	2,176 (654)	2,039 (601)	2,054 (607)
Alcohol, g/day [median (IQR)]	5.5 (0.9-15.2)	6.0 (1.3-16.8)	5.7 (1.1-15.2)	4.9 (0.5-13.5)
<b>BMI, %</b>				
<25 kg/m <sup>2</sup>	53.3	48.3	55.1	54.4
25 to <30 kg/m <sup>2</sup>	34.4	38.6	33.4	32.6
≥30 kg/m <sup>2</sup>	12.4	13.1	11.5	13.0
<b>Smoking status (%)</b>				
Never	48.7	41.1	48.8	54.8
Former	27.3	27.5	28.1	25.7
Current	22.2	30.1	20.9	17.6
Unknown	1.9	1.2	0.2	1.9
<b>Physical activity (%)</b>				
Inactive or moderately inactive	52.9	49.3	51.2	58.3
Active or moderately active	45.2	47.6	46.6	41.0
Unknown	2.0	3.2	2.2	0.7
<b>Education level (%)</b>				
Primary or lower	28.1	31.0	24.3	31.7
Secondary or higher	68.1	67.3	71.3	63.8
Unknown	3.8	1.7	4.4	4.5
<b>Menopausal status and type<sup>a</sup> (%)</b>				
Premenopausal	34.7	29.5	33.2	39.9
Perimenopausal	19.8	20.6	20.6	17.9
Postmenopausal	42.8	47.6	43.6	38.9
Surgical menopause	2.8	2.3	2.6	3.3
<b>Ever use of contraceptive pill<sup>a</sup> (%)</b>				
No	37.9	33.4	36.5	42.5
Yes	59.4	58.6	61.5	56.9
Unknown	2.6	7.9	2.0	0.6
<b>Infertility problems<sup>a</sup> (%)</b>				
No	62.3	37.1	60.9	78.4
Yes	3.1	1.3	2.9	4.2
Unknown	34.6	61.6	36.2	17.4

arMED, adapted relative Mediterranean diet; BMI, body mass index; IQR, interquartile range; SD, standard deviation. <sup>a</sup>Only in women (*n* = 318,647).

was 7.8 (3.0) ranging between 4.6 (in Sweden) and 10.7 points (in Spain) (Table 1). Participants with high arMED score were more likely to be women, younger, never smoker, physically inactive/moderate inactive, and to consume less alcohol and slightly less total energy at recruitment, compared to those with a lower arMED score (Table 2). Women with

high arMED score compared to those with low, tended to be premenopausal.

We found no association between arMED score (excluding the alcohol component) and the risk of overall differentiated TC in the fully-adjusted model (HR<sub>high vs. low adherence</sub> = 0.94, 95% CI: 0.70–1.25; *p*-trend = 0.27) (Table 3). No differences



**TABLE 3** Hazard ratios (95% Confidence Intervals) for the associations between relative Mediterranean diet score (rMED), adapted rMED (arMED) and differentiated thyroid cancer (TC) risk in the EPIC study.

	N	Overall differentiated TC	Papillary TC	Follicular TC	p for heterogeneity
Cases ( <i>n</i> )		712	573	108	
arMED score (adjusted for alcohol)					0.82
Low (0–5)	108,791	1.00 (ref)	1.00 (ref)	1.00 (ref)	
Medium (6–9)	207,470	1.13 (0.88–1.45)	1.14 (0.85–1.52)	1.26 (0.70–2.27)	
High (10–16)	133,803	0.94 (0.70–1.25)	0.96 (0.70–1.33)	0.99 (0.48–2.03)	
<i>P</i> -trend		0.27	0.38	0.83	
Continuous (per unit)	450,064	0.98 (0.95–1.02)	0.99 (0.95–1.03)	0.99 (0.91–1.08)	
rMED score (not adjusted for alcohol)					0.58
Low (0–6)	121,208	1.00 (ref)	1.00 (ref)	1.00 (ref)	
Medium (7–10)	201,933	1.05 (0.84–1.32)	1.10 (0.85–1.42)	0.88 (0.51–1.51)	
High (11–18)	126,923	0.88 (0.68–1.14)	0.87 (0.65–1.17)	0.97 (0.51–1.84)	
<i>P</i> -trend		0.17	0.14	0.97	
Continuous (per unit)	450,064	0.98 (0.95–1.01)	0.98 (0.94–1.01)	0.98 (0.91–1.07)	

Cox models were stratified by sex, age at recruitment, study center, and adjusted for total energy intake (kcal/day, continuous), body mass index (kg/m<sup>2</sup>, continuous), smoking status, alcohol (g/day, continuous, when applied), education level, and physical activity. In addition, in women, they were further adjusted for menopausal status and type, ever use of oral contraceptives, and history of infertility problems.

were observed in associations by TC subtype (*p*-value for heterogeneity = 0.82). No interactions were found for sex, smoking status, BMI, and alcohol intake. No statistically significant differences were observed in the associations between arMED score and differentiated TC risk by tumor stage, country-incidence rate, and European region (Supplementary Table 1). Similar non-statistically significant results were observed in women only and in the sensitivity analysis excluding the TC cases diagnosed within the first 2-years of follow-up (Supplementary Table 1).

A non-statistically significant inverse relationship between rMED score (including the alcohol component) and overall differentiated TC (HR<sub>high vs. low adherence</sub> = 0.88, 95% CI: 0.68–1.14; *p*-trend = 0.17), especially against papillary TC risk (HR<sub>high vs. low adherence</sub> = 0.87, 95% CI: 0.65–1.17; *p*-trend = 0.14) was observed (Table 3). In the analysis of each component of MD, we found an inverse association between low meat intake and differentiated TC risk (HR<sub>low vs. high adherence</sub> = 0.81, 95% CI: 0.67–0.99) (Table 4). The HR for moderate vs. non-moderate alcohol intake was 0.88 (95% CI 0.72–1.03). The other components were not related to differentiated TC risk.

## Discussion

Adherence to MD, measured by arMED score (without the alcohol component) was not associated with the risk of differentiated TC in this large European prospective cohort study (*n* = 450,064) with a long follow-up (mean = 14.1 years), and a relatively high number of cases (*n* = 712). The results were also non-statistically significant in all sub-analyses. However, there was a statistically non-significant inverse relationship with

rMED (including the alcohol component), probably driven by the inverse trend with alcohol intake and the positive association with meat intake.

In our longitudinal study, we did not find a clear association of differentiated TC risk with MD adherence. Whereas, in an US population-based case-control study, a tendency for an inverse association between a dietary pattern high in fruits and vegetables and risks of both overall and papillary TC were observed (31). Similarly, a traditional Polynesian dietary pattern characterized by a high consumption of fish, seafood and fruits, and low consumption of meat was inversely related, but was not statistically significant, with overall and papillary TC risk (32). In a Greek case-control study, inverse associations were found between the risk of overall and papillary TC and three dietary patterns rich in fresh fruit, raw vegetables, and mixed raw vegetables and fruits. Contrarily, a dietary pattern rich in fish and cooked vegetables, which is a dietary habit of Mediterranean populations, showed a higher risk of follicular TC (33). In a cross-sectional study, a high adherence to MD correlated with lower circulating levels of triiodothyronine (T3) and thyroxine (T4), but not with thyroid-stimulating hormone (TSH) (34). However, associations of TC with hypo- or hyperthyroidism and thyrotoxicosis are weaker and less consistent. High concentrations of free T4, TSH and the T4/T3 ratio were related to a higher differentiated TC risk in a small Canadian case-control study (35). Nevertheless, in a previous EPIC analysis, only low levels of TSH and high levels of thyroglobulin were associated with a higher differentiated TC risk, but not plasma concentrations of either T3 or T4 (36).

Except meat and a suggestive association for alcohol, none of the other components presumed to fit MD were related to differentiated TC risk in our analysis. In previous EPIC analyses,

TABLE 4 Hazard ratios (95% Confidence Intervals) of the association between each component of Mediterranean diet (MD) and differentiated thyroid cancer risk in the EPIC study.

rMED components (g/day per 2,000 kcal)	Median (33–67th percentiles)	0 point at rMED	1 point at rMED	2 points at rMED	P-trend
Vegetables	167.7 (125.9–221.1)	1.00 (ref)	0.99 (0.81–1.21)	0.89 (0.71–1.11)	0.26
Fruits	193.1 (135.3–265.0)	1.00 (ref)	1.08 (0.88–1.32)	1.07 (0.86–1.31)	0.60
Legumes	4.8 (0.8–11.3)	1.00 (ref)	1.01 (0.82–1.26)	0.94 (0.74–1.19)	0.57
Cereals	170.4 (138.8–204.3)	1.00 (ref)	0.98 (0.81–1.18)	0.92 (0.75–1.12)	0.39
Olive oil	0.0 (0.0–0.8)	1.00 (ref)	1.08 (0.85–1.39)	1.19 (0.94–1.50)	0.14
Fish	17.9 (10.2–27.7)	1.00 (ref)	1.10 (0.89–1.36)	1.20 (0.95–1.51)	0.13
Meat	94.1 (74.5–114.5)	1.00 (ref)	0.95 (0.79–1.13)	0.81 (0.67–0.99)	0.04
Dairy	286.0 (205.9–386.0)	1.00 (ref)	0.93 (0.77–1.12)	0.86 (0.71–1.05)	0.15
Alcohol (categorical)	5.6 (2.1–10.9)	1.00 (ref)		0.88 (0.75–1.03)	

rMED, relative Mediterranean diet score. Each component was calculated as a function of energy density (g/2,000 kcal per day) and then divided into tertiles of intakes (except for olive oil and alcohol). In the rMED score, for five of the six components that positively reflect Mediterranean diet: fruits (including nuts and seeds), vegetables (excluding potatoes), legumes, fish (including seafood), and cereals, points of 0–1–2 were assigned to the intake tertiles. For olive oil, 0 was assigned to non-consumers, 1 for subjects below the median intake and 2 for subjects equal or above this median. For meat and dairy products, which negatively reflect Mediterranean diet, 2–1–0 points were assigned to the first, second and third intake tertiles, respectively. Alcohol was scored dichotomously assigning 2 points for moderate consumption (sex-specific cut off points: 5–25 g per day for women and 10–50 g per day for men) and 0 points for intakes outside this range. Cox models were stratified by sex, age at recruitment, study center, and adjusted for total energy intake (kcal/day, continuous), body mass index (kg/m<sup>2</sup>, continuous), smoking status, alcohol (except for the alcohol model), education level, physical activity. In addition, in women they were further adjusted for menopausal status and type, ever use of oral contraceptives, and history of infertility problems.

similar null results were observed with the consumption of fruit and vegetables (37). Likewise, a meta-analysis using 19 case-control studies found no association with the intake of fruit and vegetables including cruciferous vegetables, which have been studied in more detail due to their content of goitrogens (38). Fish is a rich natural source of iodine which is essential for thyroid function. A meta-analysis of six case-control studies suggested that consumption of fish may decrease the risk of TC in iodine deficient areas, but not in iodine-rich areas (38). No association with fish intake was reported in a previous EPIC analysis, where very low or very high iodine intakes are rare (39). Intake of grains was not related to TC risk in a meta-analysis of three case-control studies (38). Although anti-cancer effects of olive oil and its compounds are proposed (11), neither olive oil or its compounds were associated with differentiated TC risk in previous EPIC analyses (28, 40). Similar to our findings, the incidence of TC was not related to either dairy products or calcium intake in the NIH-AARP Diet and Health Study, a large US cohort (41). Finally, our results on alcohol are broadly in agreement with a previous EPIC analysis (24) and a meta-analysis of observational studies (42), where moderate alcohol intake was associated with lower risk of TC.

In the current study, low consumption of meat was associated with a 19% lower risk of differentiated TC compared with high consumption. Only a few studies have assessed the direct role of meat intake in TC risk (17). Some classes of meat such as poultry, lamb and pork were positively associated with TC risk in case-control studies conducted in Kuwait (43), Greece (33), and the US (44), but not in Sweden and Norway (45). Potential underlying mechanisms may be related

to the concentrations of haem iron and the formation of N-nitroso compounds in meats, especially in red and processed meats (46). Indeed, nitrate can inhibit iodine uptake by the thyroid (17), dysregulate thyroid hormone production and result in thyroid tumor onset (47). Another potential mechanism of action could be the formation of heterocyclic amines and polycyclic aromatic hydrocarbons, which are well-known human mutagens/carcinogens (48). Therefore, the role of meat consumption in thyroid carcinogenesis merits further investigation.

Several limitations of this study should be considered. Dietary data derived from self-reported information relying on participants' memory is prone to measurement error. Dietary data were measured only at recruitment and do not reflect longitudinal changes in dietary intake. Nevertheless, an influence of dietary changes during the pre-diagnostic period of TC is unlikely, since sensitivity analyses excluding incident cases diagnosed within the first 2 years of follow-up were similar to the entire follow-up. Both arMED and rMED scores also have limitations, as a similar weight is given to each component and the foods within them, but not all may have equivalent effects on health or TC risk. Our risk estimates were adjusted for several confounding factors; however, we cannot rule out the possibility of residual confounding by other unmeasured factors. For instance, medical history of benign thyroid diseases, a well-established risk factor for TC was not available in EPIC. The strengths of our study are its prospective design, the relatively large number of TC cases (except for follicular TC subtype), and the wide variation in MD adherence, allowing sufficient statistical power for subgroup analyses. We also minimized any

potential bias due to overdiagnosis by stratifying the analysis into countries with high or low incidence rates and into associations with low- or high-risk TC at diagnosis.

## Conclusions

In summary, our study showed no association between adherence to arMED score and differentiated TC risk. However, a potential inverse trend with rMED was suggested, potentially driven by the consumption of a low amount of meat and a moderate amount of alcohol. Future research is required to confirm this potential association with meat intake and to evaluate which type of meat (i.e., red meat, processed meat, poultry, etc.) is responsible for these suggested harmful effects. Lastly, replication and meta-analysis of our findings with other prospective studies is required to further elucidate a possible association with MD adherence.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. For information on how to submit an application for gaining access to the EPIC data and/or biospecimens, please follow the instructions at <http://epic.iarc.fr/access/index.php>.

## Ethics statement

The studies involving human participants were reviewed and approved by Ethical review board of the International Agency for Research on Cancer (IARC). The patients/participants provided their written informed consent to participate in this study.

## Author contributions

RZ-R: conceptualization. AA, MSa, AE, AT, M-CB-R, NL, TT, CLe, VKa, MSc, DP, VKr, SS, RT, FR, GS, TJ, SC, CLa, MR-B, PA, JHu, MG, MA, LN, JH, KP, AH, EW, and SR: data resources. VC: statistical analysis. RZ-R: funding acquisition. FL and MF: writing—original draft preparation. SR and RZ-R: writing—review and editing. All authors have read and agreed to the final version of the manuscript.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



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## Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnut.2022.982369/full#supplementary-material>

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