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1 **High iodine dietary intake is associated with type 2 diabetes among**
2 **women of the E3N-EPIC cohort study.**

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17 Ruault, and G Fagherazzi have no conflict of interest to declare.

18

19 **Abstract.**

20 **Background:** Iodine is an essential micronutrient needed for the production of thyroid hormones.
21 Consequently, iodine insufficient and excessive intakes are associated with thyroid disorders.
22 Despite the increase in diabetes prevalence worldwide and the close relationship between thyroid
23 function and the risk of diabetes, the relationship between iodine intake and diabetes has been
24 overlooked. The objective of the present study is to investigate the link between iodine intake and
25 the risk of type 2 diabetes.

26 **Methods:** Cox proportional hazards regression models adjusted on potential confounders were
27 used to calculate the hazard ratios and 95% confidence intervals for the associations between
28 dietary iodine intake and type 2 diabetes risk among 71 264 women of the E3N-EPIC cohort.

29 **Results:** The average iodine intake in the study population was 155.6 $\mu\text{g} / \text{day}$ ($\pm 47.1 \mu\text{g} / \text{day}$).
30 After adjusting for the main risk factors for diabetes, for hypo/hyperthyroidism, as well as for
31 phosphorus intakes and consumption of dairy products and seafood, the hazard ratios (95% CI)
32 for type 2 diabetes of women in the 4th (160.7-190.5 $\mu\text{g} / \text{day}$) and 5th (190.6-596.8 $\mu\text{g} / \text{day}$)
33 quintiles groups of iodine intake were 1.27 (1.10-1.47) and 1.28 (1.07-1.53), respectively,
34 compared to women with iodine intake below the 1st quintile (29.3-116.9 $\mu\text{g} / \text{day}$).

35 **Conclusion:** This is the first study to investigate the relationship between dietary iodine intake
36 and the risk of developing type 2 diabetes. More studies are warranted to further investigate the
37 health effects of chronic high iodine intake, and in particular to investigate the biological
38 mechanisms that underlie the association between iodine intake and type 2 diabetes.

39 **Key words:** Iodine, type 2 diabetes, cohort study, E3N-Epic

41 **Introduction**

42 Iodine is an essential micronutrient needed for the production of thyroid hormones. Iodine is
43 almost completely absorbed by the small intestine and the kidney is the main route of excretion
44 (1, 2).

45 The World Health Organization (WHO)/ Food and Agriculture Organization of the United
46 Nations (FAO) recommend a daily iodine intake of 150 μg / day (equal to 2.0 μg / kg body
47 weight per 7 days) in adults (3). This value was also confirmed by the European Food Safety
48 Authority (EFSA) (4). The main sources of iodine in the diet are seafood (such as fish,
49 crustaceans, mussels, algae), eggs, dairy products, and iodine-enriched salt (4).

50 Iodine deficiency is associated with a higher frequency of goiter and hypothyroidism.
51 Conversely, high intakes of iodine can accelerate the development of thyroid disorders such as
52 hypothyroidism or hyperthyroidism, increase the incidence of autoimmune thyroiditis and
53 increase the risk of thyroid cancer (5, 6).

54 There is a close relationship between type 2 diabetes and thyroid dysfunction (7). Studies
55 have shown that thyroid dysfunction is more common in the diabetic population than in the non-
56 diabetic population and that altered thyroid function may affect glucose tolerance and worsen
57 metabolic control in people with diabetes (8, 9). Hypothyroidism is characterized by insulin
58 resistance and is associated with a reduced production of hepatic glucose (10-13). On the other
59 side, hyperthyroidism has been associated with increased insulin resistance and greatly
60 aggravates metabolic control in people with diabetes, promoting diabetic ketoacidosis (14-16).

61 Despite the increase in diabetes prevalence worldwide (17) and the close relationship
62 between thyroid function and the risk of diabetes, the association between iodine intake and
63 diabetes has been overlooked.

64 In this context, we decided to study the link between iodine intake and the risk of type 2
65 diabetes in the large E3N-EPIC cohort.

66

67 **Material and methods**

68 *The E3N-EPIC cohort*

69 E3N-EPIC is a French cohort study of 98,995 women born between 1925 and 1950 and it was
70 initiated in 1990 (18). It is the French component of the European Prospective Investigation into
71 Cancer and Nutrition (EPIC) (19), and the EPIC-InterAct sub-study (interaction of genetic and
72 lifestyle factors on the incidence of type 2 diabetes) (20). The data are available from postal
73 questionnaires that participants returned every 2-3 years, in addition to a database of drug
74 reimbursement that exists since 2004 from the medical records of the participants (Mutuelle
75 Générale of National Education). The average response rate for each of the eleven questionnaire
76 cycles was 83% and < 3% of the women never responded to a follow-up questionnaire. All
77 women signed letters of informed consent, according to the French National Commission for
78 Computer Data and Individual Liberty (CNIL).

79 *Study population*

80 Of the 74,522 women who responded to the diet-history questionnaire sent in 1993, we excluded
81 those who did not complete any questionnaire after the diet history questionnaire (n = 935), those
82 with an aberrant energy intake (1% and 99% extremes of the energy intake/energy expenditure
83 ratio, n = 1 467), and the cases of diabetes detected before the food history questionnaire (n =
84 856). Thus, our study population included 71,264 women, of whom 2,665 (3,7%) had developed
85 type 2 diabetes during follow-up (June 1993-February 2012).

86 *Ascertainment of type 2 diabetes*

87 Before 2004, all potential cases were identified with the follow-up questionnaires through
88 self-reporting of diabetes, diabetes diet, diabetes drugs, and hospitalization for diabetes. All
89 potential cases were then contacted and asked to answer a diabetes-specific questionnaire that
90 included questions on the circumstances of diagnosis (year of diagnosis, symptoms, biological
91 exams, fasting, or random glucose concentrations at diagnosis), diabetes therapy (prescription of
92 diet or physical activity, list of glucose lowering drugs taken), last measures of fasting glucose
93 and Hb1Ac levels.

94 Potential diabetes cases were finally validated if they declared at least one of these
95 criteria:

96 (1) fasting plasma glucose ≥ 7.0 mmol/l; random glucose ≥ 11.1 mmol/l at diagnosis;

97 (2) self-report of glucose lowering medication use;

98 (3) last values of fasting glucose or HbA1c concentrations ≥ 7.0 mmol/l or ≥ 7 %;

99 After 2004, all potential cases were identified through the drug reimbursement insurance
100 database: women reimbursed at least twice for glucose lowering medications within one year
101 period were classified as validated cases of diabetes.

102 Within the E3N cohort to date diabetes cases have been validated up to the year 2012.

103 *Evaluation of iodine intake*

104 Usual diet over the previous year was assessed by a validated 208-items diet-history
105 questionnaire in 1993, structured according to the French meal pattern. Questions were asked
106 about all times of the day when food or drinks were consumed, from breakfast to after-dinner
107 snacks, thus including all food or drink intakes between meals, such as appetizers before lunch or
108 dinner. The validity and reproducibility of the questionnaire have been previously described (21).

109 Foods were converted to macro- and micronutrients using a food composition table
110 derived from the official French food composition table (CIQUAL) (22), and supplemented

111 where necessary by the McCance and Widdowson tables (23). Daily dietary iodine intakes were
112 then estimated for each woman in the study.

113 *Statistical analysis*

114 The contribution of different food groups to the total iodine intake was calculated.

115 Due to the strong correlation between energy and micronutrient intake, iodine intake, as
116 well as intakes of all micronutrients, was energy adjusted using the residual method (24, 25).

117 Cox multivariable regression models, with age as the time scale, were used to estimate
118 hazard ratios (HR) and 95% confidence intervals (95% CI) for T2D associated with dietary
119 iodine intake. Follow-up started at the age the dietary questionnaire was completed, and ended at
120 the age of the first of the following events: diagnosis of diabetes, death, or loss to follow-up.

121 Women were classified into quintile groups according to energy adjusted iodine intake,
122 and the lowest quintile was used as the reference category in the models.

123 We first performed a univariate analysis (model 0), followed by model 1, that was
124 adjusted for physical activity (metabolic equivalent (MET)/week), body mass index (BMI,
125 kg/m²), education level (less than 12 years, between 12 and 14 years, more than 14 years), family
126 history of diabetes (yes/no), hypertension (self-reported or use of blood pressure lowering drugs:
127 yes vs. no), hypercholesterolemia (self-reported blood cholesterol >6.2 mmol/l or use of
128 cholesterol lowering drugs: yes vs. no), hyper or hypothyroidism (yes/no), and smoking status
129 (non-smoker, former smoker, smoker). The model was corrected for adherence scores to the
130 healthy dietary pattern and the western dietary pattern, both derived with principal components
131 analysis (PCA), as previously described (26).

132 We performed a second set of analyses by adding the following variables one at a time to
133 models 1 in order to identify whether they had an impact on the relationship between dietary
134 iodine intake and the risk of type 2 diabetes: retinol, omega 3 fatty acids, phosphorus, zinc,

135 calcium, sodium, copper, and iron. Variables were retained if they modified the HR for the 5th
136 quintile group for more than ± 0.05 . Taking into account the results of this second set of analyses,
137 only phosphorus was retained leading to models 2.

138 To assess the association between iodine intake and the risk of diabetes independently of
139 the main sources of iodine in our population, model 2 was adjusted for the consumption of the
140 main iodine providers, i.e. dairy products and seafood, leading to the final model (Model 3).

141 Tests for linear trends were performed for all models by assigning the median value to
142 each iodine intake quintile and modeling this value as a continuous variable. To better
143 characterize the shape of the association between iodine intake and T2D risk highlighted by the
144 final model a spline regression was performed.

145 We tested the interaction between dietary iodine intake, and BMI ($< 25 \text{ kg/m}^2$ vs. ≥ 25
146 kg/m^2) and the presence of hyper/hypothyroidism (yes/no), and when the interaction test was
147 statistically significant we performed a test of homogeneity between the groups.

148 Missing values were $< 5\%$ for all variables and were imputed with the median of the study
149 population (quantitative variables) or the mode (qualitative variables).

150 *Sensitivity analysis*

151 To test a reverse causality hypothesis, we also assessed the association between dietary
152 iodine intake and the risk of type 2 diabetes, excluding diabetes cases that occurred during the
153 first 5 years of follow-up.

154 Finally, as the residual method and the nutrient density method (nutrient intake divided by
155 total energy intake) are based on different assumptions concerning the relationship between
156 nutrient intake and total energy intake, and thus potentially provide different results, all analyses
157 were repeated using the nutrient density method.

158 All statistical tests were considered statistically significant if $P < 0.05$. Data were analyzed
159 using SAS software, version 9.4.

160

161 **Results**

162 The average iodine intake in our population was 155.6 $\mu\text{g}/\text{day}$ (± 47.1). In **Table 1** the study
163 population is described according to quintiles of iodine intake. Women with high iodine intakes
164 were younger and had higher BMI than those with low iodine intakes. Increasing iodine intake
165 was associated with increasing percentages of incident type 2 diabetes cases and of
166 hyper/hypothyroidism cases.

167 The main contributors to iodine intake in our population were dairy products and seafood,
168 with 34.8% and 14.5% of the total iodine intake, respectively (**Table 2**). Water (8.8%), cereal
169 products (8.6%) and eggs (7.6%) were the next most important sources of iodine.

170 On average every woman was followed for 13.4 (± 2.9) years, for a total of 958 359
171 person-years. High iodine intakes were associated with a higher risk of developing type 2
172 diabetes, even after adjusting for the main confounding factors (**Table 3**). Model 1, which was
173 adjusted for the main risk factors for diabetes and hyper / hypothyroidism, showed an increased
174 risk of type 2 diabetes for iodine intakes in the 4th and 5th quintile groups compared to the 1st
175 quintile group. Indeed the HRs (95% CI) for quintiles 4 and 5 were 1.25 (1.10-1.43) and 1.26
176 (1.11-1.43), respectively.

177 Phosphorus was the only variable, among those tested, which had an impact on the
178 relationship between iodine intake and the risk of type 2 diabetes modifying the HR for the 5th
179 quintile group for more than ± 0.05 (**Supplemental Table 1**). In model 2, i.e. model 1
180 additionally adjusted for phosphorus intakes, the HRs (95% CI) for the 4th and 5th quintile groups
181 were 1.21 (1.06-1.40), and 1.17 (1.01-1.38), respectively (**Table 3**).

182 Finally, model 3, which corresponds to model 2 further adjusted for dairy products and
183 seafood consumption, highlighted an increased risk of type 2 diabetes from the 4th quintile of
184 iodine intake compared to the 1st quintile group. The HRs (95% CI) for 4th and 5th quintile groups
185 were respectively 1.27 (1.10-1.47) and 1.28 (1.07-1.53) (Table 3).

186 There was a linear component of trend across quintiles of iodine intake ($p_{\text{trend}} 0.006$)
187 starting from the 3rd quartile group, which appears clearly from the graph obtained from spline
188 regression model (Figure 1).

189 There was no effect modification of the association between iodine intake and risk of type
190 2 diabetes by BMI or the presence of hyper / hypothyroidism ($p_{\text{interaction}} = 0.25$ and $p=0.32$,
191 respectively).

192 *Sensitivity analysis*

193 To test the hypothesis of reverse causality between iodine intake and the risk of type 2
194 diabetes, we excluded the 392 cases of diabetes detected during the first 5 years of follow-up.

195 We also re-analyzed model 4 using the nutrient density method on all micronutrients. The
196 results obtained with these two models were not different from the results of the initial model 4
197 (data not shown).

198

199 **Discussion**

200 In our population, high iodine intake is associated with an increased risk of type 2 diabetes. To
201 our knowledge, this is the first study that investigates the relationship between dietary iodine
202 intake and the risk of developing type 2 diabetes. The relationship appears linear and is
203 associated with a significant increase in risk from the 4th quintile of iodine intake (i.e. above
204 160.7 $\mu\text{g/day}$). The association was stable across the various tested models, i.e. adjustment for the
205 main potential confounders and sensitivity analyses.

206 *Biological mechanisms*

207 Iodine intake has mainly been studied in relation to its capacity of interfering with the thyroid
208 function; nevertheless, the observed association with type 2 diabetes can be supported by two
209 main potential biological mechanisms.

210 First, we can hypothesize a direct effect of iodine on glucose metabolism and insulin
211 resistance, although biological studies to support this theory are currently missing. Up to date,
212 most studies have focused on the effects of chronic iodine deficiency on the human organism, but
213 very few focused on high dietary intake of iodine, which seems to be the case in our population.

214 The second possible explanation is that the association between iodine intake and type 2
215 diabetes is actually mediated by the presence of undiagnosed thyroid dysfunction. A previous
216 study estimated that the mean prevalence of undiagnosed hypo- or hyperthyroidism in Europe is
217 4.94% (4.75%–5.13%) and 1.72% (1.66%–1.88%), respectively, with a clear female
218 predominance (8.12% vs 5.19%), especially regarding hyperthyroidism (27). According to that
219 study, 50% of cases of hypo- and hyperthyroidism remain undiagnosed. Comparably, the
220 American Association of Clinical Endocrinologists (AACE) estimated that in the United States
221 approximately 13 million people, or 4.78% of the population, have undiagnosed thyroid
222 dysfunction (28). It is known that excess iodine can lead to thyroid dysfunction and in particular
223 to hyperthyroidism, and that hyperthyroidism is associated with insulin resistance and impaired
224 glucose metabolism (14, 15). This may explain the association found in the present study, i.e. an
225 increased risk of developing type 2 diabetes when the mean iodine consumption exceeds 160 µg
226 per day.

227 *Strengths and limitations*

228 Our study presents some limitations. Iodine dietary intakes were estimated through the use of
229 self-administrated questionnaire, thus it is possible that the total amount of iodine could be

230 underestimated. Moreover, the dietary estimates are based on a single questionnaire, thus dietary
231 habits changes could not be taken into account leading to possibility for misclassification of
232 exposure. However, as the study is prospective, any effects are likely to be non-differential and
233 would lead to an attenuation of the true association. The fact that our study population includes
234 only women can be considered as a minor limitation due to the fact that few studies have reported
235 differences in T2D risk factors between sexes, although biological mechanisms may differ
236 between men and women.

237 Finally, the iodine intake in the present work does not take into account iodine-enriched
238 salt. However, this should not have a big impact on the total intake as the added salt (cooking salt
239 and voluntary addition salt), in western countries, accounts for less than 20% of the total salt
240 intake (29, 30) of which, in France, less than 50% is enriched with iodine (31). Nevertheless, this
241 lack of information on iodine-enriched salt suggests that the iodine intake of the study population
242 is probably underestimated. The true association between dietary iodine intake and type 2
243 diabetes may therefore be stronger than reported in the present study.

244 Our study has also several strengths. The response rate remains very high even after 20
245 years of follow-up, and the questionnaires are carefully completed by the participants (as shown
246 by satisfactory results in validation studies and questionnaire response rates), thus ensuring high
247 reliability. All participants are members of the MGEN, which provides access to comprehensive
248 medical and administrative data. The large size of the study population and the prospective
249 design of the E3N-EPIC cohort allowed us to perform sensitivity analyses while retaining
250 sufficient statistical power to detect associations and make a reverse causation bias unlikely. We
251 analyzed only validated cases of type 2 diabetes, based on a well-defined validation algorithm,
252 which reduces the risk of false negatives or false positives. Finally, detailed information on
253 potential confounders was collected, thus minimizing the risk of residual confounding.

254 *Conclusion*

255 Most studies in the literature focus on the health effects of iodine deficiency. Nevertheless, the
256 increased accessibility to seafood due to the improvement in conservation and distance
257 transportation, suggests that iodine deficiency in a developed country such as France is less
258 frequent than in previous periods. In our population, the mean iodine intake is above the
259 recommended nutritional intake despite the fact that the estimated intake is probably
260 underestimated. Our work highlights for the first time a higher risk of type 2 diabetes with high
261 iodine intake. The study should be replicated in other populations with high iodine intake and
262 potentially on other cardiometabolic health outcomes, in order to have a better overview of the
263 health impact of this increasingly consumed nutrient.

264

265

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273

274 Authors' Statement of Contributions: FRM conceived and designed the study. FRM, TH and GF
275 performed the statistical analysis. FRM drafted the original manuscript. All authors contributed to
276 the interpretation of data discussed in the manuscript, revised the manuscript and approved its
277 final version.

278

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Table 1. Characteristics (% or mean (SD)) of the study population according to quintile groups of dietary iodine intake (n=71 264). The E3N-EPIC cohort

Variables	Quintile groups of dietary iodine intake				
	1 (n=14253)	2 (n=14252)	3 (n=14254)	4 (n=14252)	5 (n=14253)
Iodine intake (µg/day)	98.93 (14.21)	128.25 (6.33)	149.57 (6.25)	174.34 (8.51)	227.17 (35.59)
Non dietary variables					
Age (years)	53.58 (6.84)	53.02 (6.72)	52.77 (6.69)	52.56 (6.53)	52.5 (6.5)
BMI (kg/m²)	22.36 (2.95)	22.66 (2.97)	22.87 (3.07)	23.02 (3.20)	23.52 (3.53)
Family history of diabetes (%)	10.15	11.30	10.66	11.58	11.91
Hypercholesterolemia(%)	38.03	38.08	39.17	38.56	35.49
Hypertension (%)	13.27	12.59	13.37	13.44	14.07
Physical activity (METs h/week)	46.58 (52.59)	47.66 (51.95)	47.87 (43.02)	50.62 (49.27)	54.16 (54.63)
Smoking					
Current (%)	15.05	13.28	13.25	12	13.47
Former (%)	30.93	32.56	33.11	33.10	33.28
Education					
< 12 years of (%)	14.10	12.88	13.36	13.59	15.26
12 - 14 years (%)	49.76	51.25	52.09	51.83	50.19
> 14 years (%)	36.14	35.88	34.55	34.58	34.55
Hyper/ hypothyroidism (%)	14.61	15.16	15.86	16.50	17.44
Type 2 diabetes incident cases (%)	2.88	3.12	3.69	4.18	4.82
Dietary variables					
Energy intake without carbohydrates and alcohol (kcal/day)	901.06 (200.66)	1066.61 (212.15)	1177.26 (234.27)	1292.17 (259.6)	1516.11 (332.18)
Alcohol intake (g ethanol/ day)	10.83 (13.61)	11.03 (13.15)	11.49 (13.48)	11.89 (14)	12.73 (14.99)
Carbohydrates intake (g/day)	190.88 (54.41)	216.86 (58.35)	233.52 (62.54)	252.02 (68.33)	281.71 (77.7)
Vitamin A intake (µg/day)	806.58 (794.9)	1032.36 (929.31)	1197.3 (1072.21)	1364.87 (1186.45)	1711.11 (1519.81)

Omega 3 intake (g/day)	1.10 (0.33)	1.33 (0.36)	1.49 (0.40)	1.66 (0.45)	2.03 (0.61)
Phosphorus intake (mg/day)	1064.06 (198)	1286.03 (189.01)	1443.86 (203.95)	1616.57 (226.76)	1976 (346.11)
Zinc intake (mg/day)	8.83 (2.33)	10.3 (2.36)	11.35 (2.5)	12.43 (2.69)	14.62 (3.25)
Calcium intake (mg/day)	695.07 (167.72)	888.09 (167.15)	1029.08 (189.04)	1188.17 (219.02)	1529.38 (365.85)
Sodium intake (mg/day)	2182.04 (651.85)	2564.47 (698.01)	2808.22 (740.85)	3080.28 (810.50)	3560.35 (962.18)
Copper intake (mg/day)	2.38 (0.96)	2.66 (1.04)	2.87 (1.16)	3.06 (1.25)	3.52 (1.51)
Iodine intake/total energy intake	0.06 (0.01)	0.07 (0.01)	0.07 (0.02)	0.08 (0.02)	0.09 (0.02)
Iron intake (mg/day)	11.72 (2.75)	13.33 (2.88)	14.45 (3.1)	15.61 (3.42)	17.79 (4.06)

Table 2. Percentage contribution of the main food groups to the total dietary iodine intake. The E3N-EPIC cohort

Food group	Contribution to the total iodine intake (%)
Dairy products	34.82
Seafood	14.53
Water	8.78
Cereal products	8.58
Eggs	7.64
Hot beverages (the, café...)	5.89
Fruit and vegetables	5.40
Others	14.36

Table 3. Hazard ratios (95% CI) estimated by Cox multivariable regression models for the risk of incident type 2 diabetes according to quintile groups of dietary iodine intake ($\mu\text{g}/\text{day}$) estimated by the residual method (n=71 264). The E3N-EPIC cohort

Daily intake	Quintile groups of dietary iodine intake ($\mu\text{g}/\text{day}$)					P trend
	1 st	2 nd	3 rd	4 th	5 th	
	29.3-116.9	117.0-138.9	139.0-160.7	160.8-190.6	190.7-596.8	
Model 0	REF	1.13 (0.99-1.29)	1.20 (1.05-1.36)	1.44 (1.27-1.64)	1.70 (1.50-1.92)	<0.0001
Model 1	REF	1.11 (0.97-1.27)	1.11 (0.97-1.27)	1.25 (1.10-1.43)	1.26 (1.11-1.42)	<0.0001
Model 2	REF	1.10 (0.96-1.26)	1.09 (0.95-1.25)	1.21 (1.06-1.40)	1.17 (1.01-1.38)	0.0009
Model 3	REF	1.12 (0.97-1.28)	1.12 (0.97-1.29)	1.27 (1.10-1.47)	1.28 (1.07-1.53)	0.006

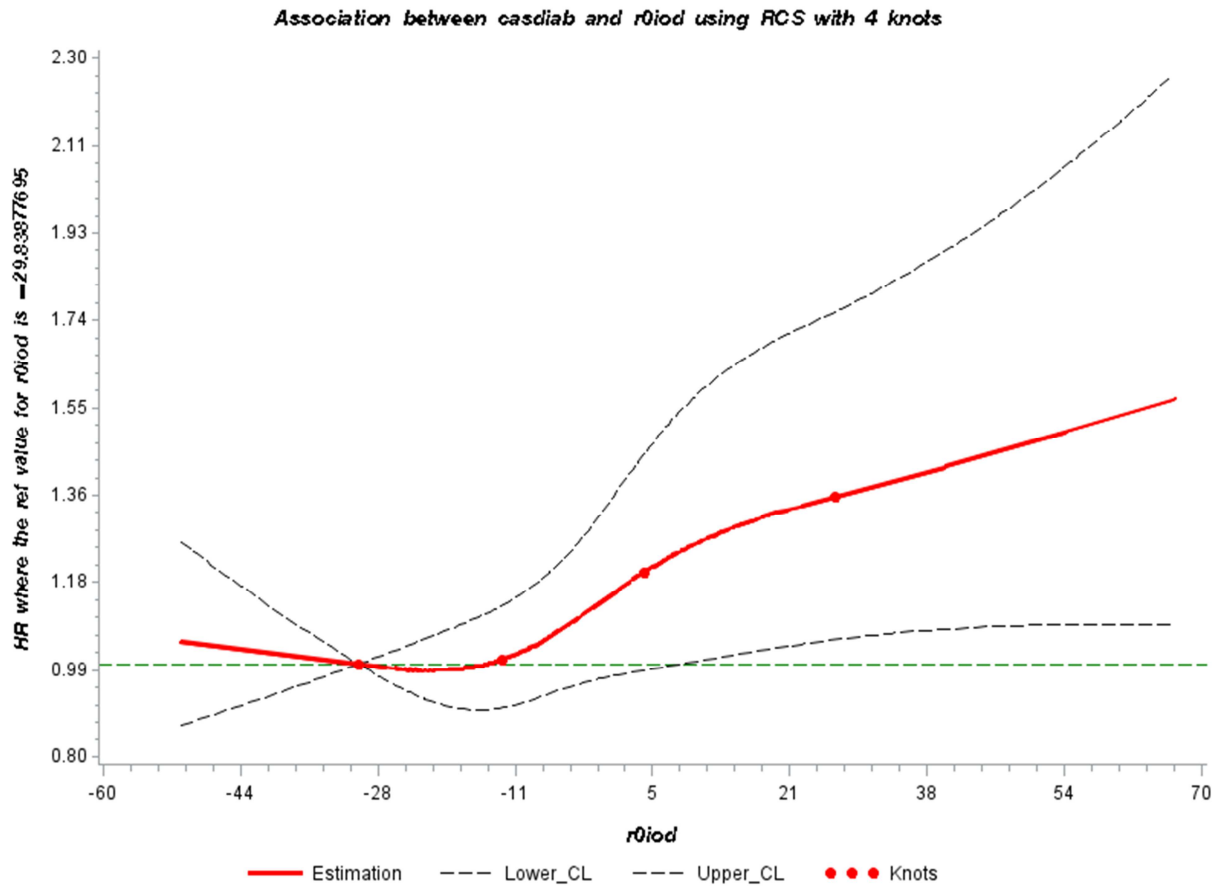
Model 0: univariate

Model 1: adjusted for physical activity (MET/week), BMI (kg/m²), education level (less than 12 years, between 12 and 14 years, more than 14 years), hypertension (yes/no), family history of diabetes (yes/no), hypercholesterolemia (yes/no), hyper / hypothyroidism (yes/no), smoking status (non-smoker, former smoker, smoker) adherence to the Western diet (as continuous variable) and adherence to the Mediterranean diet (as continuous variable).

Model 2: Model 1 + phosphorus intake ($\mu\text{g}/\text{day}$)

Model 3: Model 2 + dairy products and seafood consumption (gr/day)

Figure 1. Spline regression model between the dietary iodine intake ($\mu\text{g}/\text{day}$) estimated by the residual method and the risk of type 2 diabetes ($n=71\,264$). The E3N-EPIC cohort.



Spline regression (4 knots): the model was adjusted for physical activity (MET/week), BMI (kg/m^2), education level (less than 12 years, between 12 and 14 years, more than 14 years), hypertension (yes/no), family history of diabetes (yes/no), hypercholesterolemia (yes/no), hyper / hypothyroidism (yes/no), smoking status (non-smoker, former smoker, smoker) adherence to the Western diet (as continuous variable) and adherence to the Mediterranean diet (as continuous variable), phosphorus intake ($\mu\text{g}/\text{day}$), dairy products consumption and seafood consumption (gr/day)

Online supporting material.

Supplemental Table 1: Results of the stepwise approach: hazard ratios (95%CI) for the risk of incident type 2 diabetes according to quintiles of dietary iodine intake ($\mu\text{g}/\text{day}$) adding one by one the dietary variables to model 1 and model 2. The E3N-EPIC cohort

	Quintile groups of dietary iodine intake ($\mu\text{g}/\text{day}$)					P trend
	1 st	2 nd	3 rd	4 th	5 th	
Daily intake	29.3-116.9	117.0-138.9	139.0-160.7	160.8-190.6	190.7-596.8	
Model 1 + vitamin A	REF	1.10 (0.96-1.26)	1.10 (0.96-1.26)	1.24 (1.09-1.41)	1.22 (1.07-1.40)	0.002
Model 1 + omega 3	REF	1.10 (0.96-1.26)	1.11 (0.97-1.26)	1.24 (1.11-1.42)	1.23 (1.11-1.41)	0.002
<u>Model 1 + phosphorus</u>	REF	1.10 (0.96-1.26)	1.11 (0.95-1.25)	1.21 (1.06-1.40)	1.18 (1.00-1.38)	0.050
Model 1 + zinc	REF	1.10 (0.96-1.26)	1.10 (0.96-1.26)	1.23 (1.08-1.40)	1.20 (1.05-1.40)	0.005
Model 1 + calcium	REF	1.12 (0.97-1.28)	1.12 (0.98-1.29)	1.27 (1.11-1.47)	1.28 (1.09-1.51)	0.003
Model 1 + sodium	REF	1.10 (0.97-1.27)	1.11 (0.97-1.27)	1.25 (1.10-1.42)	1.23 (1.08-1.41)	0.001
Model 1 + copper	REF	1.11 (0.97-1.27)	1.11 (0.97-1.27)	1.25 (1.10-1.43)	1.24 (1.09-1.42)	0.001
Model 1 + iron	REF	1.11 (0.97-1.27)	1.11 (0.97-1.27)	1.25 (1.10-1.43)	1.24 (1.08-1.42)	0.001