Iodine Deficiency and Mortality in Spanish Adults: Di@bet.es Study

Cristina Maldonado-Araque,[1,2] Sergio Valdés,[1,2] Rocío Badía-Guillén,[1] Ana Lago-Sampedro,[1,2]
Natalia Colomo,[1,2] Eduardo Garcia-Fuentes,[3] Carolina Gutierrez-Repiso,[4,5] Albert Goday,[6]
Alfonso Calle-Pascual,[2,7] Luis Castaño,[2,8,9] Conxa Castell,[10] Elías Delgado,[9,11] Edelmiro Menendez,[9,11]
Josep Franch-Nadal,[2,12] Sonia Gaztambide,[2,9,13] Joan Girbés,[14] Francisco Javier Chaves,[2,15]
Federico Soriguer,[1,2] and Gemma Rojo-Martínez[1,2]

Background: Longitudinal data assessing the impact of iodine deficiency (ID) on mortality are scarce. We aimed to study the association between the state of iodine nutrition and the risk of total and cause-specific mortality in a representative sample of the Spanish adult population.

Methods: We performed a longitudinal observational study to estimate mortality risk according to urinary iodine (UI) concentrations using a sample of 4370 subjects >18 years representative of the Spanish adult population participating in the nationwide study Di@bet.es (2008–2010). We used Cox regression to assess the association between UI at the start of the study (<50, 50–99, 100–199, 200–299, and ≥300 μg/L) and mortality during follow-up (National death registry—end of follow-up December 2016) in raw models, and adjusted for possible confounding variables: age, sex, educational level, hypertension, diabetes, obesity, chronic kidney disease, smoking, hypercholesterolemia, thyroid dysfunction, diagnosis of cardiovascular disease or cancer, area of residence, physical activity, adherence to Mediterranean diet, dairy and iodinated salt intake.

Results: A total of 254 deaths were recorded during an average follow-up period of 7.3 years. The causes of death were cardiovascular 71 (28%); cancer 85 (33.5%); and other causes 98 (38.5%). Compared with the reference category with adequate iodine nutrition (UI 100–300 μg/L), the hazard ratios (HRs) of all-cause mortality in the category with UI ≥300 μg/L were 1.04 (95% confidence interval [CI 0.54–1.98]); however, in the categories with 50–99 UI and <50 μg/L, the HRs were 1.29 [CI 0.97–1.70] and 1.71 [1.18–2.48], respectively (*p* for trend 0.004). Multivariate adjustment did not significantly modify the results.

Conclusions: Our data indicate an excess mortality in individuals with moderate-severe ID adjusted for other possible confounding factors.

Keywords: iodine, mortality, epidemiology, Spain

[1]Department of Endocrinology and Nutrition, Hospital Regional Universitario de Málaga, Instituto de Investigación Biomedica de Málaga-IBIMA, Málaga, Spain.
[2]Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Instituto de Salud Carlos III, Madrid, Spain.
[3]UGC de Aparato Digestivo, Hospital Universitario Virgen de la Victoria, Instituto de Investigación Biomedica de Málaga-IBIMA, Málaga, Spain.
[4]CIBER de Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain.
[5]Department of Endocrinology and Nutrition, Hospital Universitario Virgen de la Victoria, Instituto de Investigagión Biomedica de Málaga-IBIMA, Málaga, Spain.
[6]Department of Endocrinology and Nutrition, Hospital del Mar, Barcelona, Spain.
[7]Department of Endocrinology and Nutrition, Hospital Universitario S. Carlos de Madrid, Madrid, Spain.
[8]Hospital Universitario Cruces, BioCruces Bizkaia, UPV/EHU, Barakaldo, Spain.
[9]Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Instituto de Salud Carlos III, Madrid, Spain.
[10]Department of Health, Public Health Agency of Catalonia, Barcelona, Spain.
[11]Department of Endocrinology and Nutrition, Hospital Universitario Central de Asturias/University of Oviedo, Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain.
[12]EAP Raval Sud, Institut Català de la Salut, Red GEDAPS, Primary Care, Unitat de Suport a la Recerca (IDIAP—Fundació Jordi Gol), Barcelona, Spain.
[13]Department of Endocrinology and Nutrition, Hospital Universitario Cruces, BioCruces Bizkaia, UPV/EHU, Barakaldo, Spain.
[14]Diabetes Unit, Hospital Arnau de Vilanova, Valencia, Spain.
[15]Genomic Studies and Genetic Diagnosis Unit, Fundación de Investigación del Hospital Clínico de Valencia-INCLIVA, Valencia, Spain.

Introduction

IODINE IS A trace element that is essential for the synthesis of thyroid hormones. Iodine deficiency (ID) can lead to goiter, thyroid dysfunction, cognitive impairment, and delayed physical development (1).

Despite progress in strategies for preventing and controlling ID, ID disorders continue to be a major public health problem throughout the world. It is estimated that >2000 million people worldwide are still at risk of insufficient iodine intake, 459.7 million in Europe (2). In Spain, although the evolution of iodine nutrition in recent years has been favorable placing our country globally as with "adequate iodine nutrition," there is still evidence that a large proportion of the population remains iodine deficient (3). Moreover, there is a lack of policies concerning monitoring systems on the population iodine status, or in the prevention of ID, such as universal salt iodization, as recommended by the World Health Organization (WHO) and United Nations International Children's Emergency Fund (UNICEF) (4).

As most iodine ingested by the body is excreted in urine (90%), urinary iodine (UI) reflects recent dietary iodine intake, therefore the assessment of iodine intake is mostly based on urinary excretion. Studies have convincingly demonstrated that a profile of iodine concentrations in morning or other random urine specimens provides an adequate assessment of a population's iodine nutrition, when provided by a sufficient number of individuals (1).

Assessing an association between ID and mortality beyond its effects on thyroid function would stress the need to implement preventive strategies focused on its eradication. However, longitudinal data studying the impact of iodine nutrition on mortality are scarce.

The aim of this study was to investigate if there is an association between the state of iodine nutrition, measured as UI in a random urine sample, and the risk of total and cause-specific mortality in a representative sample of the Spanish adult population.

Materials and Methods

Population

The Di@bet.es Study is a national, cross-sectional, population-based survey conducted in 2009–2010 (5–7). A cluster sampling design was used to select participants to form a representative random sample of the Spanish population. One hundred health centers or their equivalent from all around the country were selected randomly, with a probability for selection proportional to their target population size (Fig. 1), after which 100 individuals aged ≥18 years were randomly selected from each health center. Of the eligible adults, 55.8% were evaluated, and 9.9% were excluded (because they were institutionalized, had severe disease, were pregnant, or recently delivered), resulting in a final sample of 5072 individuals.

We selected 4383 subjects for this study for whom UI measurements were available. In addition, we excluded 13 subjects on treatment with amiodarone, usually prescribed for cardiac arrhythmia, which contents a high amount of iodine in its composition. All these 13 subjects had UI concentrations >400 μg/L.

The research was carried out in accordance with the Declaration of Helsinki (8) of the World Medical Association. Written informed consent was obtained from all the participants. The study was approved by the Ethics and Clinical Investigation Committee of the Hospital Regional Universitario de Málaga (Malaga, Spain) in addition to other regional ethics and clinical investigation committees all over Spain.

Variables and procedures

The participants were invited to attend a single examination visit at their health center. Information was collected using an interviewer administered structured questionnaire, followed by a physical examination and blood and urine sampling.

Information on age, sex, educational level, smoking status, and other sociodemographic variables was obtained using
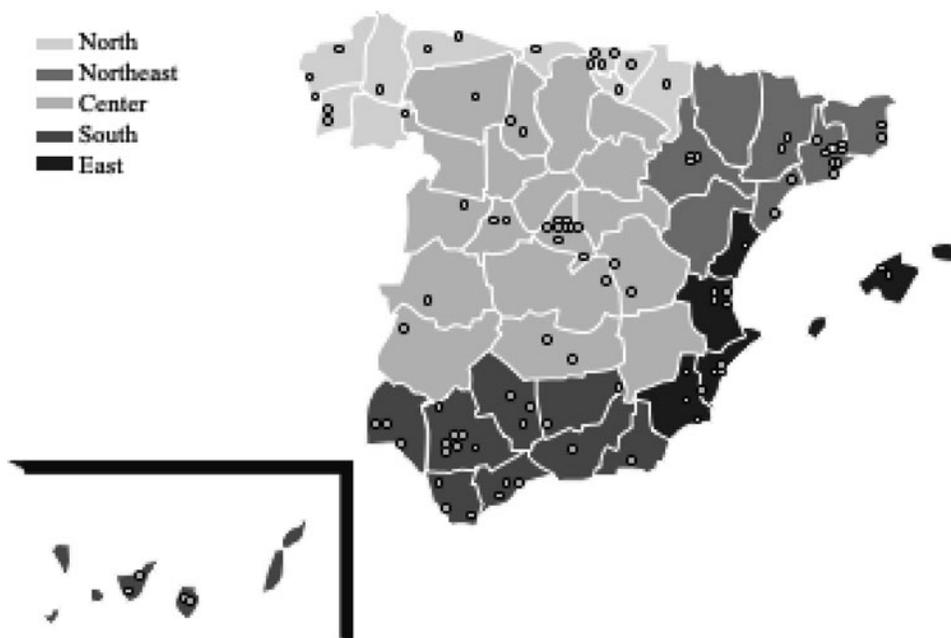

FIG. 1. Map showing the 100 clusters included in the Di@bet.es study. Geographical zones are indicated.

a questionnaire. Food consumption was determined by a 40-item food frequency questionnaire. The questionnaire included the assessment of dairy and iodinated salt consumption. Adherence to a Mediterranean diet was estimated by a modified version of a validated 14-item Mediterranean diet score (MedScore) (9). The level of daily physical activity was estimated by the short form of the International Physical Activity Questionnaire (10). Self-reported previous diagnoses of cardiovascular disease and cancer were also recorded.

Weight and height were measured by standardized methods. The body mass index (BMI) was calculated. A BMI $\geq 30 \, kg/m^2$ was considered as representing obesity (11). Blood pressure was measured using a blood pressure monitor (Hem-703C; Omron, Barcelona, Spain) after several minutes in a seated position; the mean of two measurements taken after at least two minutes apart was used for analysis. Hypertension was considered if there was a previous clinical diagnosis of hypertension, and/or systolic blood pressure was $\geq 140 \, mmHg$ and/or diastolic blood pressure was $\geq 90 \, mmHg$ (12).

Participants with baseline capillary blood glucose levels <7.8 mmol/L (measured by OneTouch® system; Lifescan, Johnson & Johnson, S.A.) and not receiving treatment for diabetes mellitus (DM) underwent a standard oral glucose tolerance test, obtaining fasting and two hours venous samples (8–10 hours fasting samples were obtained between 8:30 a.m. and 10:00 a.m.). Samples were immediately centrifuged, and the serum was frozen until analysis.

Serum glucose, triglycerides, and cholesterol were measured enzymatically and high-density lipoprotein cholesterol by a direct method. The diagnosis of DM was based on the 1999 WHO criteria (13). Hypercholesterolemia was defined as total cholesterol concentration $\geq 240 \, mg/dL$ or treatment with lipid lowering drugs (14).

Creatinine was analyzed with the modified Jaffe method (Randox Laboratories Ltd., Antrim, United Kingdom), using an A15 autoanalyzer (BioSystems, Barcelona, Spain) (15). Estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (16). CKD was defined by CKD-EPI equation–calculated eGFR <60 mL/min/1.73 m^2 (16).

Thyrotropin (TSH), free triiodothyronine, and free thyroxine were measured by chemoluminescence in a modular analytics E170 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Thyroid dysfunction was considered in individuals on treatment with levothyroxine and/or thionamides or with TSH levels >5 mIU/L or TSH <0.2 mIU/L (6).

UI measurements and classification

UI was analyzed using the modified method of Benotti and Benotti (17). The intra- and interassay coefficients of variation of the UI assay were 2.01% and 4.53%, respectively. The UI assay was subjected to external quality assessments for the determination of iodine in urine by the Spanish Association of Neonatal Screening and by the Ensuring the Quality of Iodine Procedures program. All samples were analyzed in the Research Laboratory of the Hospital Regional Universitario de Málaga (Spain).

UI levels were classified according to current WHO, UNICEF, and the Iodine Global Network (formerly International Council for the Control of Iodine Deficiency Disorders) recommendations (1): <50 μg/L moderate-severe deficiency, 50–99 μg/L mild deficiency, 100–199 μg/L adequate, 200–299 μg/L above requirements, and ≥ 300 μg/L excessive. UI levels in this population (Di@bet.es) and its conditioning factors have been previously reported (7).

Follow-up and assessment of fatal events

Mortality data were ascertained on December 31, 2016 by the National Spanish Statistics Institute (Instituto Nacional de Estadística), from information on death certificates from the national death registry. The cause of death was coded according to the International Classification of Diseases, Tenth version ICD-10 of the WHO (18). Cardiovascular death was defined with codes I00–I99 ("diseases of the circulatory system") or R96 ("other sudden death, cause unknown"). Death due to cancer was defined with the codes C00-D48 ("neoplasms").

Statistical analysis

The study population was grouped into four categories according to their UI concentrations (1). The sociodemographic characteristics of the study population as well as other covariates of interest were determined in each category. The number of events (deaths) was estimated for each group calculating the mortality rates for each 1000 inhabitant-years (95% confidence interval [CI]). We used the Kaplan–Meier curves to describe all-cause mortality according to these categories. Cox regression analysis was used to analyze the corresponding relative risks (RRs) of death, in crude models and in multivariate models. The category with UI 100–300 μg/L was used as a reference for the calculations of the RR.

As recommended, the selection of potential confounders was based on the *a priori* existing knowledge, rather than centered on statistical selection procedures (19–21). Potential confounders included in the model were age, sex, education level (no studies/basic/high school-college), area of residence (south/center/east/north/northeast), hypertension (yes/no), DM (yes/no), obesity (yes/no), CKD (yes/no), smoking (yes/no), thyroid dysfunction (yes/no), prior cardiovascular disease (yes/no), prior cancer (yes/no), hypercholesterolemia (yes/no), medscore, physical activity (low/medium/high), dairy consumption (<1 per day, 1 per day, ≥ 2 per day), and iodinated salt consumption. To assure a minimum ratio of events per independent variable of 10 (22), this multivariate regression model requires a minimum of 180 events available for analyses.

Sensitivity analyses were reconducted under different assumptions: (i) excluding participants with thyroid dysfunction and (ii) excluding participants with cardiovascular disease or cancer.

All the statistical analyses were performed with IBM SPSS statistics 23.0 and Epibasic 1.0 (University of Aarhus, Nordre Ringgade, Denmark). Reported *p*-values were based on two-sided tests with statistical significance set at 0.05.

Results

Clinical characteristics of the study sample according to UI categories

The study sample comprised of 4370 individuals with a mean age of 50.4 years (age range 18–93 years) and 57.4% were female. Mean and median UI concentrations in the population at baseline were 134.7 ± 83 μg/L and 117.1 μg/L,

respectively. Figure 2 shows the distribution of UI concentrations in the study sample. The distribution is concordant with an iodine-sufficient population with no evidence of significant overiodization. However, 29.7% of the population had mild ID (UI 50–99 μg/L) and 9.7% had ID that was moderate-severe (UI <50 μg/L).

Table 1 shows the clinical characteristics and the distribution of the covariates in the sample according to UI concentrations. There were no significant differences in the age and sex between groups. There were small differences in the education level, with a higher proportion of individuals without studies in both the categories with very low (<50 μg/L) and excessive UI (≥300 μg/L). There was also an imbalance in the distribution of the area of residence across the categories. The prevalence of cardiovascular risk factors and CKD was similar between groups. Also, there were no significant differences regarding adherence to med diet, physical activity, or in the proportion of individuals reporting a previous history of cardiovascular disease or cancer. There was however a clearly higher proportion of individuals with thyroid dysfunction in the excessive UI (≥300 μg/L) category than in the rest of the categories. As expected, there was a strong association between the UI levels and the consumption of iodine salt and dairy products.

UI categories and mortality

Overall, a total of 254 deaths in 31.901 person-years of follow-up were recorded. The causes of death were cardiovascular, 71 (28%); cancer, 85 (33.5%); and other causes, 98 (38.5%). The mean duration of follow-up was 7.3 years.

Table 2 shows the mortality rates and hazard ratios (HRs) for total mortality, and cardiovascular and cancer mortality in the participants grouped in categories according to their UI concentrations. In unadjusted models, participants with moderate-severe ID (<50 μg/L) had a 70% relatively high hazard of all-cause mortality compared with those with adequate iodine nutrition (100–300 μg/L). There was also a nonsignificant intermediate increase in the hazard (29%) in

the category with mild ID (50–99 μg/L) and a highly significant dose–response relation across the categories with normal (100–300 μg/L), mild (50–99 μg/L), and moderate-severe (<50 μg/L) ID (p for trend 0.004). There was no significant increase in the mortality hazards in the category with excessive UI (≥300 μg/L). Multivariate adjustment of the analyses did not induce any modification in the results.

Figure 3 includes the results of sensitivity analyses conducted repeating the cox regression models for total mortality in different scenarios (all population, excluding prevalent thyroid dysfunction and excluding prevalent cardiovascular disease or cancer). Apart from some minor changes, the direction of the results was similar, and in all scenarios, a mortality excess in the moderate-severe ID category could be observed.

Figure 4 graphically shows the Kaplan–Meier curves for total mortality incidence according to UI groups, showing an increase in the mortality curve in the category with UI <50 μg/L during follow-up, which was already apparent after four years of follow-up.

Specific analysis by causes of mortality was limited due to the low number of estimates available. Acknowledging this limitation, the analysis suggested a marked increase in cardiovascular mortality, associated with ID (Table 2). Compared with the reference, cardiovascular mortality crude HRs were increased 2.1-fold in the category with mild ID (50–99 μg/L), whereas moderate-severe ID (<50 μg/L) was associated with a 2.4-fold increase. Again, there was a highly significant dose–response relation in the hazards across these categories (p = 0.002). At higher UI (>300 μg/L), there was also a 42% increase in the mortality risk, although the results were not significant. After multivariate adjustment, only moderate-severe deficiency (<50 μg/L) was significantly associated with an increase in the mortality risk (RR 2.38 vs. reference), although a significant trend remained.

Unlike what was observed for cardiovascular mortality, no significant associations between UI and cancer mortality were observed, neither in the crude nor in the multivariate models (Table 2).
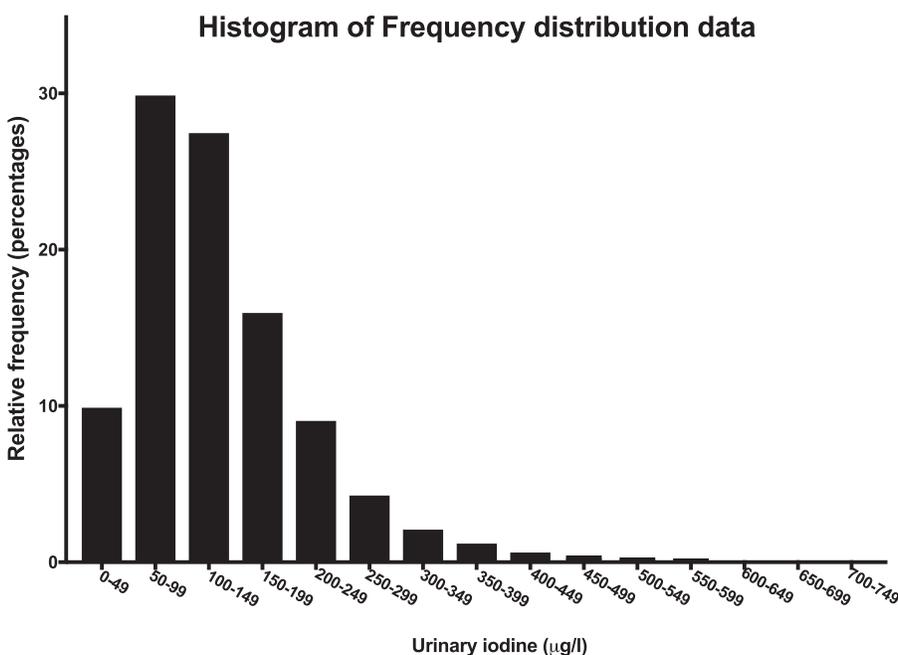

FIG. 2. Distribution of the UI concentrations in the study sample (*n* = 4370). UI, urinary iodine.

TABLE 1. BASELINE CHARACTERISTICS OF THE STUDY SAMPLE ACCORDING TO URINARY IODINE CONCENTRATIONS

	Urinary iodine (µg/L)				p Value for difference
	<50	50–100	100–300	>300	
Number	426	1299	2454	191	
Age (years)	50.3 ± 16.4	49.9 ± 16.5	50.5 ± 16.9	52.6 ± 16.5	0.217
Sex (female) (%)	57.0	57.0	57.4	60.7	0.804
Educational level (%)					
No studies	16.3	12.2	11.4	18.3	
Basic	47.2	49.4	47.9	50.3	0.004
High school-college	36.6	38.4	40.5	31.4	
Area of residence (%)					
North	22.1	10.5	8.2	12.6	
Center	25.1	26.1	28.0	21.5	<0.001
Northeast	16.4	17.2	16.9	18.3	
East	11.7	11.1	14.4	17.8	
South	24.6	35.2	32.4	29.8	
Smoking (%)	25.9	26.2	26.0	25.1	0.992
Hypertension (≥140/90) (%)	47.3	45.6	43.8	47.6	0.366
Diabetes (WHO 1999) (%)	15.5	14.1	12.4	13.1	0.209
Obesity (%)	29.2	30.2	31.5	27.7	0.553
Hypercholesterolemia (≥240 mg/dL) (%)	21.2	25.4	26.2	25.3	0.207
CKD (eGFR <60 mL/min) (%)	5.9	7.6	6.7	7.0	0.642
Thyroid dysfunction (%)	8.1	7.1	11.9	24.2	<0.001
Mediterranean diet score	7.8 ± 1.8	7.7 ± 1.8	7.8 ± 1.7	7.9 ± 1.8	0.375
Physical activity (SF-IPAQ) (%)					
Low	39.2	44.3	42.4	41.4	
Medium	38.9	34.6	32.8	37.2	
High	21.9	21.1	24.8	21.5	0.053
Previous cardiovascular disease (%)	5.2	6.6	7.4	7.9	0.358
Previous history of cancer (%)	1.2	0.8	1.3	1.6	0.652
Iodized salt intake (%)	32.8	33.4	42.3	51.3	<0.001
Dairy consumption (%)					
<1 Per day	17.0	11.2	8.7	8.4	
1 Per day	24.3	22.3	21.0	20.9	
≥2 Per day	58.7	66.5	70.3	70.7	<0.001

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SF-IPAQ, short form of the International Physical Activity Questionnaire; WHO, World Health Organization.

Discussion

Our results, evaluating a large representative sample of the Spanish adult population with adequate iodine nutrition monitored during an average follow-up of 7.3 years, showed an association between moderate-severe ID and mortality that remained after the adjustment for multiple potential confounders. To the best of our knowledge, this association had not been previously described, and, if confirmed, could have important public health implications.

Despite our results being limited due to the low number of estimates available, the specific analyses by causes of mortality suggest that the association between ID and mortality was mainly driven by cardiovascular causes. This fact, along with the apparent independence of the association with the presence of thyroid dysfunction at baseline, makes us hypothesize about possible extrathyroid mechanisms with impact on the cardiovascular system as possible mechanisms of this association.

In this sense, several mechanisms could be involved:

(i) Iodine has well-known antioxidant and anti-inflammatory effects (23). Micromolar amounts of iodine decrease damage by free oxygen radicals and increase the total antioxidant status in human serum

(24). It is also well established that povidone–iodine exerts an anti-inflammatory action by neutralizing radical oxygen species (25). Previous experimental studies conducted by our group (26) demonstrated that a daily dose of 100, 200, or 300 mg of iodide in the form of potassium iodide for six months did not modify thyroid function, but had some anti-inflammatory effects; on day 60 of the treatment, UI concentration correlated with C-reactive protein (r 0.461, $p = 0.018$), and with the changes produced in α1-antitrypsin (r 0.475, $p = 0.014$) and ceruloplasmin (r 0.599, $p = 0.001$). Another previous study by our group also demonstrated that iodine is involved in the regulation of oxidative stress and adiponectin levels in human breast milk (27).

(ii) Hemodynamic effects: Iodinated soluble radiographic contrast media induce vasodilatation, which is associated with increased blood flow, decreases in vascular peripheral resistance, and variations in systemic and peripheral arterial blood pressure (28). It is not clear if iodine itself can exert some of these effects. It is noteworthy that iodine infusions have been shown to reduce heart damage by as much as 75% in a mouse model of acute myocardial infarction (29).

TABLE 2. COX PROPORTIONAL HAZARD RATIOS (95% CONFIDENCE INTERVALS) FOR ALL-CAUSE, CARDIOVASCULAR, AND CANCER MORTALITY ACCORDING TO URINARY IODINE CATEGORIES (WORLD HEALTH ORGANIZATION–UNITED NATIONS INTERNATIONAL CHILDREN'S EMERGENCY FUND)*

	Urinary iodine (µg/L)				p for trend[a]
	<50	50–99	100–299	≥300	
Patients (n)	426	1299	2454	191	
All-cause mortality					
Deaths (n)	36	84	124	10	
Mortality/1000 person-years [CI]	**11.8 [8.2–16.3]**	8.9 [7.1–11.0]	6.9 [5.8–8.2]	7.2 [3.4–13.2]	
RR crude [CI]	**1.71 [1.18–2.48]**	1.29 [0.97–1.7]	1 (reference)	1.04 [0.54–1.98]	0.004
RR multivariate [CI]	**1.71 [1.12–2.61]**	1.28 [0.94–1.75]	1 (reference)	1.07 [0.54–2.15]	0.010
Cardiovascular mortality					
Deaths (n)	11	30	27	3	
Mortality/1000 person-years [CI]	**3.6 [1.8–6.4]**	**3.2 [2.1–4.5]**	1.5 [1.0–2.2]	2.2 [0.4–6.3]	
RR crude [CI]	**2.40 [1.19–4.85]**	**2.10 [1.25–3.54]**	1 (reference)	1.43 [0.43–4.72]	0.002
RR multivariate [CI]	**2.38 [1.05–5.40]**	1.82 [1.00–3.32]	1 (reference)	1.58 [0.46–5.42]	0.011
Cancer mortality					
Deaths (n)	11	26	44	4	
Mortality/1000 person-years [CI]	3.6 [1.8–6.4]	2.8 [1.8–4.0]	2.5 [1.8–3.3]	2.9 [0.8–7.4]	
RR crude [CI]	1.47 [0.76–2.85]	1.12 [0.69–1.82]	1 (reference)	1.17 [0.42–3.25]	0.314
RR multivariate [CI]	1.33 [0.62–2.82]	1.07 [0.63–1.83]	1 (reference)	1.31 [0.46–3.74]	0.443

*Reference (1).

Multivariate: age, sex, education level (no studies/basic/high school-college), hypertension (yes/no), diabetes (yes/no), obesity (yes/no), ckd (yes/no), smoking (yes/no), thyroid dysfunction (yes/no), prior cardiovascular disease (yes/no), prior cancer (yes/no), hypercholesterolemia (yes/no), area of residence (south/center/east/north/northeast), Med_score, SF-IPAQ (low/medium/high), dairy consumption (<1 per day, 1 per day, ≥2 per day), iodinated salt consumption (yes/no)

In bold $p < 0.05$ versus UI 100–299 µg/L (reference).

[a]p for trend across categories with UI 100–299 µg/L (reference), 50–99 µg/L, and <50 µg/L.

RR, relative risk; CI, 95% confidence interval; UI, urinary iodine.

(iii) Antiatherosclerotic effects: ID has also been associated with dyslipidemia (30), and iodine treatment has been shown to reduce serum lipid levels (31,32). Animal studies, performed as early as the 1930s, clearly demonstrated that iodine compounds can prevent the development of atherosclerosis in rabbits (33,34). Also at the epidemiological level, low iodine levels have been associated with an increased prevalence of coronary artery disease in adults without thyroid dysfunction (35).

Although some of these mechanisms could theoretically explain an effect of ID in the cardiovascular system independently of thyroid function, it is also noteworthy that
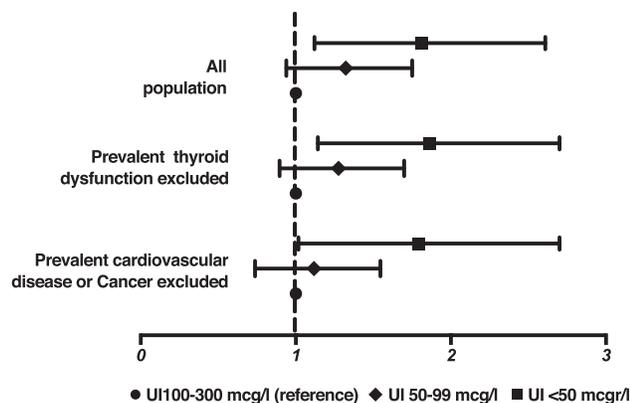

FIG. 3. All-cause mortality according to UI categories in different scenarios. Data show relative risk for total mortality and 95% confidence interval in multivariate-adjusted cox models.

although we controlled our analyses by prevalent thyroid dysfunction at baseline, we cannot disregard an increased incidence of thyroid dysfunction during follow-up as a mediator of the association between ID and mortality. Moreover, even in subjects with normal thyroid hormone levels, ID could be associated with insufficient cardiac tissue levels of thyroid hormones, as has been addressed in animal models in studies by Escobar del Rey et al. (36).

Finally, different studies have suggested an association between ID and breast and prostate cancer (37–39). This antineoplastic effect has been hypothesized as being caused by different mechanisms and pathways. The oxidized iodine dissipates the mitochondrial membrane potential, thereby triggering mitochondrion-mediated apoptosis. Another mechanism would be iodolipid formation and the activation of peroxisome proliferator-activated receptors type gamma, which triggers the BAX-caspase apoptotic pathway (40). Although in our study we did not observe an increase in cancer mortality, the low statistical power of the analysis does not allow us to draw any definitive conclusion.

It is noteworthy that the descriptive design of our study does not allow us to confirm or reject any of these hypotheses to explain our results that we present as merely speculative.

To the best of our knowledge, there is only one previous epidemiological study assessing the association between iodine status and mortality with a prospective design and interestingly, the results are not concordant with our study (41). Inoue et al. (41) estimated mortality risks according to UI concentrations utilizing a nationally representative sample of 12,264 adults aged 20–80 years enrolled in the National Health and Nutrition Examination Survey III over a median follow-up of 19.2 years. According to their results,

FIG. 4. The Kaplan–Meier curves for total mortality incidence according to UI concentrations. Color images are available online.
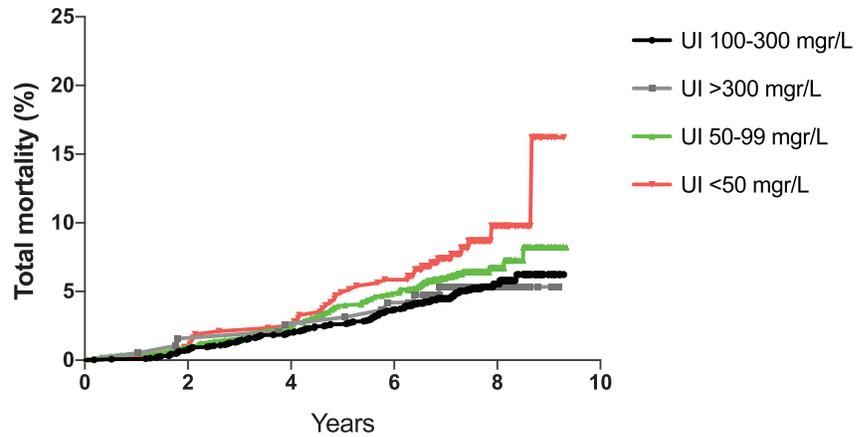
participants with excess iodine exposure (UI >400 μg/L) were at a higher risk of all-cause mortality compared with those with adequate iodine nutrition (HR, 1.19; [CI 1.04–1.37]), whereas low UI concentration was not associated with an increased mortality.

Differences in the background population, including different iodine nutrition status in the United States compared with the Spanish population, differences in diet, could partially account for these differences. Also, it is known that the susceptibility of individuals to excessive or insufficient iodine intake is dependent on the geographical area of residence, and this information was not available in the Inoue *et al.* (41) study, hence analyses could not be suitably adjusted accordingly. It also seems to us that a long follow-up of 19.2 years makes more likely that a shift to an increased intake of iodine in the ID group during time could have occurred, potentially biasing the mortality estimates toward null. There are also other differences in the statistical approach between the studies.

Although some of these factors could be considered partially explanatory, we do not have a definitive explanation to account for the differences in the results of these two studies, and clearly more data from other prospective studies are necessary.

It is interesting to note that we were not able to study the group with very high UI (≥400 μg/L), associated with an increased mortality in the Inoue *et al.* (41) study, due to the very low number of subjects in that group. so Therefore, we cannot discard or confirm an increased mortality in this segment of the population.

Our study has several limitations. First, iodine status was estimated only from a single spot urine measurement. While UI in spot samples is a well-validated biomarker of iodine status for population assessments (1), individual assessment is challenging, and probably requires repeated samples to account for intraindividual day-to-day variability (42–44). Future studies should try to overcome this limitation by repeating UI assessments in at least part of the study population.

Second, we excluded from analyses any participants under amiodarone treatment, but could not exclude the possibility that participants had received iodinated contrast and both patients affected by cancer or cardiovascular disease may have had iodinated contrast computed tomography scans or angiography. Prevalent diagnosis of cancer or cardiovascular disease was introduced in the analysis as a covariate. Also, sensitivity analyses excluding participants with these diagnoses showed similar results.

Third, unlike the Inoue *et al.* (41) study, we were not able to adjust the results by sodium intake, but as iodine intake is strongly linked to sodium intake (in the form of iodized salt) (45) and sodium excess is associated with a higher risk of hypertension and cardiovascular disease (46), not including this variable in the analyses could, if anything, most likely generate a bias toward null.

Finally, the main limitation lies in the relatively small sample size with limited number of events available for analyses and in the observational cohort nature of the design, hence we cannot establish causal associations or exclude residual confounding factors.

In conclusion, our study shows an association between ID and mortality in Spanish adults, which seems to be driven mostly by cardiovascular causes. The discrepancy with previous studies, and the limited sample size and number of events, stress the need for further studies to clarify the relation between iodine status and mortality and cardiovascular disease in the general population.

Author Disclosure Statement

There is no competing financial interest that could be perceived as prejudicing the impartiality of the research reported.

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Address correspondence to:
Sergio Valdés, MD, PhD
Department of Endocrinology and Nutrition
Hospital Regional Universitario de Málaga/
Universidad de Málaga
IBIMA
Plaza del Hospital Civil s/n
Malaga 29009
Spain

E-mail: sergio.valdes@hotmail.es