Effect of Excess Iodine Intake from Iodized Salt and/or Groundwater Iodine on Thyroid Function in Nonpregnant and Pregnant Women, Infants, and Children: A Multicenter Study in East Africa

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Background: Acute excess iodine intake can damage the thyroid, but the effects of chronic excess iodine intake are uncertain. Few data exist for pregnant and lactating women and infants exposed to excessive iodine intake.
Methods: This was a multicenter cross-sectional study. At study sites in rural Kenya and urban Tanzania previously reporting iodine excess in children, urinary iodine concentration (UIC), thyrotropin, total thyroxine, and thyroglobulin (Tg) were measured in school-age children (SAC), women of reproductive age, pregnant (PW) and lactating women, and breast-feeding and weaning infants. In a national study in Djibouti, UIC was measured in SAC and PW. At all sites, daily iodine intake was estimated based on UIC, and iodine concentration was measured in household salt and drinking water.
Results: The total sample size was 4636: 1390, 2048, and 1198 subjects from Kenya, Tanzania, and Djibouti, respectively. In Kenya and Tanzania: (i) median UIC was well above thresholds for adequate iodine nutrition in all groups and exceeded the threshold for excess iodine intake in SAC; (ii) iodine concentrations >40 mg of iodine/kg were found in approximately 55% of household salt samples; (iii) iodine concentrations ≥10 μg/L were detected in 9% of drinking water samples; (iv) Tg was elevated in all population groups, but the prevalence of thyroid disorders was negligible, except that 5–12% of women of reproductive age had sub-clinical hyperthyroidism and 10–15% of PW were hypothyroxinemic. In Djibouti: (i) the median UIC was 335 μg/L (interquartile range [IQR] = 216–493 μg/L) in SAC and 265 μg/L (IQR = 168–449 μg/L) in PW; (ii) only 1.6% of Djibouti salt samples (n = 1200) were adequately iodized (>15 mg/kg); (iii) the median iodine concentration in drinking water was 92 μg/L (IQR = 37–158 μg/L; n = 77). In all countries, UIC was not significantly correlated with salt or water iodine concentrations.
Conclusions: Although iodine intake was excessive and Tg concentrations were elevated, there was little impact on thyroid function. Chronic excess iodine intake thus appears to be well tolerated by women, infants, and children. However, such high iodine intake is unnecessary and should be avoided. Careful evaluation of contributions from both iodized salt and groundwater iodine is recommended before any review of iodization policy is considered.

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Introduction

IODINE IS A CONSTITUENT of thyroid hormone and is essential for normal growth and development. Iodine intake and thyroid gland function have a U-shaped relationship, that is, both inadequate and excessive intake may affect normal thyroid function and increase the risk of morbidity (1–3). Optimal population iodine nutrition is defined as a median urinary iodine concentration (UIC) of 100–299 μg/L for school-age children (SAC) and 150–499 μg/L for pregnant women (PW) (4). Universal salt iodization (USI) has had remarkable success worldwide, and although 112/143 countries with data in SAC report UIC within the optimal range, iodine intake is excessive in 11 countries (5).

Excess iodine intake may arise from the consumption of excessive seaweed, dietary supplements, or over-iodized salt (6–11). Recent data from Somalia (8), without a salt iodization program in place, suggest iodine-rich groundwater may be another cause of excess intake. Distinct geographical pockets of naturally occurring elevated water iodine concentrations have been documented in a number of countries (6,11–14). Iodine intake in excess of daily requirements is generally well tolerated by the healthy thyroid (9,15). However, both acute and chronic excessive iodine intake have been associated with thyroid disorders in susceptible individuals (9,15,16), but data are scarce, particularly in vulnerable populations such as pregnant and lactating women, and infants (9).

Thyroglobulin (Tg), the thyroid-specific glycoprotein on which iodine is stored and thyroid hormone is formed, can be measured in serum or on dried blood spots (DBS) and is a sensitive biomarker of iodine status (17–19). Tg is recommended in addition to spot urine samples for UIC in population surveys of iodine status (4). Collection of DBS-Tg is a field-friendly method (20), and DBS-Tg is a sensitive biomarker for borderline excessive iodine intake in SAC and PW (2,3).

This study aimed to assess the effects of a chronic exposure to iodine intake above recommended levels on Tg, thyroid function, and subclinical and overt thyroid disorders in women, infants, and children. To do this, two regions were selected in Kenya and Tanzania that previously reported high iodine intake in SAC, and a national survey was performed in Djibouti, a country suspected to have iodine-rich groundwater due to its location in Northeast Africa (11). The hypothesis was that chronic excess iodine intake in these regions would cause an increase in thyroid disorders in the population.

Methods: Kenya and Tanzania

Study design and study sites

A cross-sectional study was conducted of six population groups at sites in rural Eastern Kenya (Kibwezi, Makueni County) and urban Tanzania (Kinondoni District, Dar es Salaam) with previously documented iodine excess in SAC (median UIC >300 μg/L) (2,21).

Kenya. Since its inception in 1970, salt iodization in Kenya has been remarkably successful, with a 99.5% household coverage of iodized salt recorded in 2014 (22). In 2003–2004, the national median UIC in SAC was 118 μg/L (23), though intake was as high as 477 μg/L in Nairobi. In response, in 2010, the government reduced the recommended salt iodine concentration from 100 to 30–50 mg/kg (24). In 2011, the Kenyan National Micronutrient Survey reported a national median UIC of 208 μg/L (interquartile range [IQR] = 108–333 μg/L) in SAC; 30% had a UIC >300 μg/L (24), but intake varied highly nationwide. A study in Kibwezi District recorded a median UIC of 624 μg/L (IQR = 437–939 μg/L) in SAC (*n* = 342) (21); 90% had a UIC >300 μg/L, and 21% had an elevated serum Tg (>40 μg/L). Daily salt intake was estimated to be 4 g/child/day, and the mean iodine content in household salt samples was 64 mg/kg (*n* = 18), suggesting additional dietary iodine contributions from another source. Limited data on groundwater iodine concentrations in Kenya have generally recorded concentrations <10 μg/L (25,26).

Tanzania. Salt iodization was introduced in Tanzania in 1995 (27), and it was mandated at 20–80 mg/kg (28). In 2010, the national coverage of iodized salt was 82% (29), but this dropped to 64% in 2014, and coverage was uneven across the country (29). The 2010 national survey reported a median UIC in women of reproductive age (WRA) of 160 μg/L, but high intake was observed in urban areas (median UIC 375 μg/L) (30). In Kinondoni District of Dar es Salaam, the median UIC in SAC was 338 μg/L (range 6–1883 μg/L) and the geometric mean ± standard deviation (*SD*) of DBS-Tg was 17.6 ± 14.3 μg/L (2).

At both country sites, iodized salt is widely available, and bouillon cubes or powder made with iodized salt are used to flavor foods. Iodine-containing dietary supplements are generally unavailable. Subsidized fortified maize meal (vitamin A, thiamin, riboflavin, niacin, pyridoxine, folic acid, iron, and zinc) and fortified cooking oil (vitamin A) are staples in the diet.

Subjects

Following a standard protocol for both study sites, participants were recruited from six different population groups: (i) SAC (aged 6–12 years); (ii) nonpregnant non-lactating WRA (aged 18–44 years); (iii) PW (aged 18–44 years); (iv) lactating women (aged 18–44 years); (v) exclusively breastfed infants ("breast-feeding infants"; aged 0–6 months); and (vi) infants and children 7–24 months of age receiving both breast milk and complementary foods ("weaning infants"). SAC and WRA, and lactating women and breast-feeding infants were recruited as pairs where possible.

The inclusion criteria for all subjects were: (i) residence at the study site for ≥12 months; (ii) apparently healthy and no reported treatment for chronic disease; (iii) no family or personal history of thyroid disease; (iv) no exposure to iodine-containing contrast agent or medication within the last year (since birth if <12 months, except for iodine disinfectant used at birth). Additional criteria for women and infants

stated that WRA should not currently be pregnant or breast-feeding, and PW or lactating women must have had a healthy, singleton pregnancy. Infants (breast-feeding infants and weaning infants) must have been born at full term (gestation 38–42 weeks) from a singleton pregnancy, and not have a weight-length Z-score <–3 or mid-upper arm circumference (MUAC) <115 mm (31). Any infant identified as such was excluded from the study and referred for medical assistance. PW were recruited at all stages of gestation; mean $\pm SD$ gestational age at enrolment was 27 ± 8.5 weeks for Kenyan women and 25 ± 7.0 weeks in Tanzania ($p = 0.24$). Sample sizes were greater for trimesters two and three compared to the first trimester (Kenya: 8.4%, 31.3%, and 60.2%; Tanzania: 5.3%, 53.4%, and 41.2%; of total sample sizes for trimesters 1, 2 and 3, respectively).

As a population-based study with a cross-sectional sampling frame, the study estimated the number of subjects needed to establish the median UIC around which the population varies according to Lemeshow *et al.* (32), and that needed to estimate the proportion of SAC with an elevated Tg on DBS (>40 μg/L) using the equation of Naing *et al.* (33). Using previous data from Kinondoni, Tanzania (2), and allowing for a 15% margin for participant withdrawal and loss to follow-up, it was calculated that a sample size of 300 participants per group per study site would allow these outcomes to be estimated with 90% confidence and 5% error.

Ethical approval was obtained from the Ethics Review Committee of the ETH Zurich (Zurich, Switzerland), the National Institute for Medical Research in Tanzania, and the Kenyatta University Ethics Review Committee in Kenya. Participants were recruited following information sessions: in schools, parents of students in applicable class age groups were invited to attend an information session; in participating health centers and dispensaries, a similar session was held at the start of pre- or antenatal clinics on appropriate days. Participation was voluntary, and written informed consent was obtained from every participant at entry to the study (parent or legal guardian for breast-feeding infants and weaning infants; parent and child for participation of SAC). All collected data were anonymized before analysis. In Kenya, participants were recruited from three health centers, one hospital, and three schools in Kibwezi District; in Tanzania, participants were recruited from four health dispensaries and five schools in Kinondoni District.

Study procedures

The study was conducted between January and April 2016.

Anthropometrics. Upon entry to the study, anthropometric assessment of all participants was conducted using standard methods (34). Participants were instructed to remove shoes where applicable, empty pockets, and wear light clothing. Body weight was measured to the nearest 0.1 kg using a Seca digital scale (Seca 874) or Seca baby scale (Seca 384) calibrated with standard weights (Seca, Hamburg, Germany). Length or height was measured to the nearest 0.1 cm using a pull-down measuring tape or UNICEF length board (UNICEF Supply Division). Head circumference was measured to the nearest 0.1 cm using a commercial tape measure. Weight and height were measured for all participants, and head circumference for infants and children.

Weight-for-age (WAZ) and length or height-for-age (HAZ) Z-scores were calculated for infants and children based on the World Health Organization (WHO) age- and sex-specific Child Growth Standards (35), using Anthro and AnthroPlus v3.2.2 (World Health Organization, Geneva, Switzerland). Body mass index (BMI) was calculated for WRA and lactating women by dividing the weight (kg) by the square of the height (m^2). At inclusion, WLZ was estimated using age- and sex-specific WHO growth charts (35) for all breast-feeding infants, and the MUAC of weaning infants was measured using a 6- to 60-month-old MUAC tape (UNICEF Supply Division). Median Z-scores in included infants were otherwise all greater than the WHO cutoff of <–2 to indicate low WAZ or HAZ (35).

Questionnaire. A questionnaire was administered to all participants to ascertain general dietary habits, including general consumption of native iodine-rich foods, knowledge and use of iodized salt for both participant and household, use of dietary supplements, and cigarette smoking in women. Additional questions for breast-feeding infants and their lactating mothers covered iodine exposure at birth and feeding practices, and for weaning infants, weaning practices and complementary food intake, particularly weaning foods fortified with iodine.

Spot urine sample. A spot urine sample was collected from all participants at any time of day except the first morning void in order to determine iodine status by UIC. SAC, WRA, PW, and lactating women were given a plastic cup and were asked to provide around 20 mL of fresh midstream urine. Where mother–child pairs were sampled, samples were collected on the same day. Samples from breast-feeding infants were collected using a pad collection system (Sterisets Newcastle Urine Collection Pack, Sterisets International B.V., The Netherlands). The pad was placed inside a disposable nappy and checked regularly until wet with urine (but not soiled with feces) when it was then removed and >3 mL of urine expressed. Mothers of weaning infants were invited to use the same system for their infants or, if preferred, supplied with a clean plastic cup to collect approximately 20 mL of midstream urine. The urine samples were aliquoted (at least 1 mL per aliquot) into three 2.0 mL Eppendorf tubes (Eppendorf, Hamburg, Germany) without filtration, transported in a cool box from the place of the collection to the local storage freezer, transported frozen to the laboratory, and stored frozen at −20°C until analysis.

Estimated iodine intake. Daily iodine intake was estimated using the UIC for each population group except for lactating women (36), using average urine volumes of 1 L for SAC, 1.5 L for WRA, 1.8 L for PW (37), and 500 mL for both infant groups (38). Dietary iodine excretion was set at 90% (37).

DBS. Trained laboratory technicians collected finger-prick samples from SAC and women or heel-prick samples from infants onto DBS filter paper collection cards (IDBS-226; PerkinElmer, CT). Blood spots contained 50 μL of whole blood. After collection, cards were dried at room temperature and placed in sealed plastic bags with a desiccant, and then stored frozen at −20°C until analysis. DBS-Tg,

DBS-thyrotropin (TSH), and DBS-total thyroxine (TT4) were measured to assess prevalence of thyroid dysfunction.

Breast milk. To assess breast milk iodine concentration (BMIC) and provide a complete assessment of the iodine status of lactating women, a breast milk sample was collected from lactating women enrolled in Kenya. A 10 mL foremilk sample was obtained by manual expression into a plastic container (39). Breast milk samples were transported cold from the place of collection, separated into aliquots, frozen at −20°C, and shipped frozen from the study sites to the ETH Zurich for analysis.

Salt. A household salt sample for determination of iodine content was collected from WRA–SAC pairs enrolled in the study at both sites. During pre-study information sessions held at the respective schools, parents were requested to bring approximately 50 g of household salt to their visit in a clean plastic container. The salt samples were stored tightly closed at room temperature without drying until analysis.

Drinking water. In Kenya, 20 mL of household water was collected that was usually drunk and used for culinary purposes. WRA–SAC pairs were asked to bring a sample in a clean plastic container. The water samples were aliquoted into three 2.0 mL Eppendorf tubes and frozen at −20°C until analysis. Furthermore, groundwater sources were opportunistically sampled in Kenya in a 25 km radius around the study site, including from bore holes, wells, springs, a local river, and piped water outlets, reportedly fed from a natural source approximately 10 km from the study site (Umani Springs, Chyulu Hills National Park) and treated with chlorine disinfectants. No samples could be taken directly from this source, uniquely from the outlets. Water was taken from each site in triplicate in 20 mL clean, iodine-free plastic containers, from which each sample was aliquoted into three 2.0 mL Eppendorf tubes without filtration and frozen at −20°C until analysis. Bore holes were pumped and allowed to run for a few minutes before sampling to obtain fresh water. In Tanzania, a drinking water sample was collected from a subset of 30 students per school ($n = 114$). Selection of these students was made with the help of teachers in order to permit collection of water from groundwater sources in the immediate vicinity of the school. Samples were aliquoted as previously described.

Methods: Djibouti

Study design and study sites

The study in Djibouti was cross-sectional and nationally representative. Recruitment was from five districts each from both within and outside of Djibouti City. SAC were selected from representative households each assigned an identification number in the 10 districts; PW were recruited from health center records ($n = 130$ for Djibouti City, 13 health centers; $n = 100$ for the rest of the country, 20 per district). Sampling and study design was in accordance with the National Statistics and Demographic Studies Department of Djibouti (Direction de la Statistique et des Études Démographiques [DISED]).

Subjects

In total, 985 SAC aged 6–13 years and 213 PW aged 18–43 years in their second or third trimester were recruited.

Study procedures

Samples were collected between November and December 2015. Sample collection did not coincide with the rainy period, though the Republic of Djibouti is an arid country with an annual rainfall of <200 mm (40). The study was conducted in participation with the Nutrition Service of the Republic of Djibouti Ministry of Health, Mother and Child Health Department (Ministère de la Santé, Direction de la Santé de la Mère et de l'Enfant), Service Nutrition), which granted approval for conduct of the study, and DISED.

Spot urine sample. Following written informed consent, a spot urine sample was collected from all participants at any time of day except the first morning void. Participants were asked to provide approximately 20 mL of fresh, midstream urine into a plastic cup. Samples were aliquoted into three 2.0 mL Eppendorf tubes without filtration, transported in a cool box from the place of collection to the local storage freezer, transported frozen to the laboratory, and stored frozen at −20°C until analysis.

Salt. All subjects were requested to provide a sample of household salt to assess iodine content. Participants were requested to bring approximately 50 g of household salt to their visit in a clean plastic container. The salt samples were stored tightly closed at room temperature, without drying, until analysis.

Drinking water. Seventy-seven potable water samples were collected from drinking water outlets in five regions (Djibouti city-Arta, Obock, Tadjourah, Dikhil, and Ali Sabieh) to assess iodine content. Samples were representative of the nine potential types of drinking water in Djibouti. Approximately 25 mL of water was collected from each source into clean plastic containers, which was later aliquoted unfiltered into three 2.0 mL Eppendorf tubes and frozen at −20°C until analysis. Bore holes were allowed to run for a few minutes before sampling to obtain fresh water.

Laboratory analyses

All sample collection materials (urine, salt, and water collection material; test tubes; and urine collection pads) were tested for iodine contamination (41).

Urinary iodine, salt iodine, and water iodine concentrations. The Tanzania Food and Nutrition Centre (TFNC; Dar es Salaam, Tanzania) measured iodine concentrations in urine and salt from Tanzania and Djibouti using a modified version of the Sandell–Kolthoff method (42), with an inter-assay variation of 18.3% for lower controls ($41 \pm 7.5\,\mu g/L$; $n = 28$), 10.5% for mid-range controls ($88 \pm 9.2\,\mu g/L$; $n = 28$), and 7.7% for high controls ($180 \pm 14\,\mu g/L$; $n = 28$). All other urine, salt, and water samples were measured at the Human Nutrition Laboratory (Institute of Food, Nutrition and Health, ETH Zurich), using the same method, with an inter-assay variation for lower controls of 4.6% ($67 \pm 3\,\mu g/L$; $n = 71$) and

for high controls of 3.2% (205 ± 7 μg/L; $n = 71$). The same ETH Zurich laboratory-specific control material was analyzed at the TFNC with an inter-assay variation of 9.2% for lower controls (62 ± 6 μg/L; $n = 18$) and 3.5% for high controls (190 ± 7 μg/L; $n = 18$). Both laboratories successfully participate in the Program to Ensure the Quality of Urinary Iodine Procedures (U.S. Centers for Disease Control and Prevention, Atlanta, GA), including its quarterly external validation.

A subset of water samples was externally validated by the Inorganic Geochemistry laboratories at the British Geological Survey (Nottingham, United Kingdom) by inductively coupled plasma mass spectrometry (ICP-MS; Agilent 8900; Agilent Technologies, Santa Clara, CA), with high agreement between methods ($R = 0.999$, $p < 0.001$).

Adequate iodine status in SAC, WRA, breast-feeding infants, and weaning infants was defined as a median UIC ≥100 μg/L (4). In PW, adequacy was set at ≥150 μg/L and excess at ≥500 μg/L (4). In SAC, excessive iodine intake was defined as a median UIC ≥300 μg/L; no such threshold has been defined for nonpregnant adults or infants. UIC was not used to determine iodine status in lactating women (36).

The salt iodine concentration was defined as low at <15 mg/kg, adequate at 15–40 mg/kg, and high at >40 mg/kg (4); water with iodine ≥10 μg/L was considered as iodine concentrated (43).

Thyroid function. DBS-Tg was measured at the Human Nutrition Laboratory of the ETH Zurich using a DBS-Tg enzyme-linked immunosorbent assay, as described elsewhere (44). Serum control samples (Liquicheck Tumor Marker Control, LOT.23911, 23912, 23913; Bio-Rad, Hercules, CA) were used as standards for the DBS Tg assays. In-house DBS samples were used for quality control, and the inter-assay variation for lower controls was 18.3% (25.8 ± 4.7 μg/L; $n = 96$), 12.0% at mid-range controls (51.7 ± 6.2 μg/L; $n = 96$), and 12.7% for high controls (72.0 ± 9.1 μg/L; $n = 31$). Assay-specific reference ranges for DBS-Tg are 4–40 μg/L in SAC and 0.3–43.5 μg/L in PW, with risk of an excessive intake in that population defined as >3% of values lying above the upper threshold. No reference values for this DBS-Tg assay have been defined for nonpregnant adults or infants.

TSH and TT4 concentrations were measured at the University Children's Hospital Zurich (Swiss Newborn Screening Laboratory and Children's Research Center, Zurich, Switzerland) using an automated time-resolved fluoroimmunoassay method and a Genetic Screening Processor (GSP) machine (2021-0010; PerkinElmer, Turku, Finland) and related GSP Neonatal TSH/T4 kits (PerkinElmer). Kit-specific controls were used for the analysis, with an intra-assay variability for TSH of 9.1% at 0.92 ± 0.08 mIU/L ($n = 26$) and 6.8% at 10.20 ± 0.69 mIU/L ($n = 30$) and for TT4 of 7.4% at 49.5 ± 3.6 nmol/L ($n = 28$), 14.0% at 106.2 ± 14.9 nmol/L ($n = 28$), and 6.0% at 221.1 ± 13.3 nmol/L ($n = 28$). American Thyroid Association (ATA) recommended thresholds (45–48) were used to adapt kit-specific laboratory reference ranges and applied to estimate the prevalence of thyroid dysfunction in the study population. For infants, SAC, and WRA, the following thresholds were used. TSH: 0–7 days, 0.1–10.5 mIU/L; 7–21 days, 0.1–5.3 mIU/L; 21–60 days, 0.1–5.0 mIU/L; 60–155 days, 0.1–4.5 mIU/L; ≥155 days, 0.1–3.7 mIU/L. TT4: 0–7 days, 114–245 nmol/L; 7–21 days, 123–170 nmol/L; 21–60 days, 84–170 nmol/L; 60–155 days, 80–

165 nmol/L; ≥155 days, 65–165 nmol/L. In the absence of reference ranges for lactating women, the adult reference range was used (0.1–3.7 mIU/L). This reference range was also applied to PW in the second and third trimesters. For PW in the first trimester, the upper limit of the DBS-TSH assay was lowered by 18% to 3.0 mIU/L following the most recent ATA recommendations (48). For DBS-TT4 in PW in gestational weeks 1–6, the assay specific normal adult reference range of 65–165 nmol/L was applied, increasing the upper limit by 5% per week from week 7 (48). From week 16, the nonpregnant adult reference range was multiplied by 1.5, and the resulting thresholds of 97.5–247.5 nmol/L were used thereafter (48). Data were recorded as being either lower than or elevated over these reference ranges. Then, the following diagnostic criteria were applied to the data to estimate the prevalence of thyroid dysfunction. Subclinical hypothyroidism: elevated DBS-TSH, normal DBS-TT4; overt hypothyroidism: elevated DBS-TSH and low DBS-TT4 or DBS-TSH >10 mIU/L and normal TT4; subclinical hyperthyroidism: low DBS-TSH and normal DBS-TT4; overt hyperthyroidism: low DBS-TSH and elevated DBS-TT4; and isolated hypothyroxinemia: normal DBS-TSH and low DBS-TT4.

BMIC. BMIC was measured at the Human Nutrition Laboratory of the ETH Zurich by multi-collector ICP-MS (Finnigan NEPTUNE; Thermo Fisher Scientific, Waltham, MA) with the use of isotope dilution analysis with ^{129}I and Tellurium for mass bias correction (39). Samples were prepared with the use of tetramethylammonium hydroxide (Tama, Kawasaki, Japan) for iodine extraction at 90°C for 180 min. Whole-milk powder standard reference material (NIST SRM1549a Whole Milk Powder; National Institute of Standards and Technology, Gaithersburg, MD) was used as an external control. The mean ± SD iodine concentration of the standard reference material ($n = 6$) was 3427 ± 80 μg/kg (CV: 2%), which is in agreement with the certified acceptable range (3040–3640 μg/kg).

Statistical analyses

Statistical analyses were performed using Microsoft Excel 2011 (Microsoft Corp., Redmond, WA) and IBM SPSS Statistics for Windows v23 (IBM Corp., Armonk, NY). UIC and DBS-Tg were the co-primary outcomes, and TSH and TT4 on DBS were the secondary outcomes. Data normality was assessed using Kolmogorov–Smirnov and Shapiro–Wilk tests, a skewness of <1, and visually using Q–Q and P–P plots; non-normal data were log-transformed where possible. Outlying data were checked for validity and corrected where possible or removed where there were obvious typographical errors (e.g., 200 cm height) that could not be resolved. Otherwise, no outliers were removed. Unless specified, all normally distributed data are described as mean ± SD, and nonparametric data are described as median (IQR). Data were bootstrapped ($n = 1000$) where applicable to obtain robust confidence intervals.

Group differences were assessed between continuous nonparametric variables using the Kruskall–Wallis test with Bonferroni correction, and by one-way analysis of variance with Bonferroni correction for data able to be appropriately log transformed. Spearman's rho was used to test nonparametric associations with ordinal data. The association between UIC and other secondary outcome parameters was

assessed using regression analyses on log data with relevant covariates. Group differences for prevalence were compared using the chi-square test, followed by the Z-test to check for significant differences between the individual values, applying Bonferroni correction. Separate subgroup analyses were undertaken in PW based on gestational week: PW who enrolled at (i) ≤20 weeks' gestation ($n = 42$ in Kenya and $n = 104$ in Tanzania), corresponding to the time before which the fetal thyroid is not capable of iodine organification, and (ii) ≤36 weeks' gestation ($n = 116$ in Kenya and $n = 300$ in Tanzania).

In Djibouti, the association between water iodine concentration and UIC was assessed where both water iodine concentration and UIC were available. To model influences on UIC in addition to potential effects of water consumption further, the distance from the coast was estimated for each location as a proxy for the potential influence of seafood consumption on iodine intake, and the potential influence of main bedrock type per location on the corresponding iodine content of the water source was investigated, applicable to traditional and drilled wells only. Rock types were taken from the Global Lithological Map (GLiM) v1.0 (University of Hamburg, Hamburg, Germany) (49). The trends between water source and iodine concentration were also evaluated at each location.

Significance was set at $p < 0.05$.

Results: Kenya and Tanzania

A total of 3438 participants from rural Kenya ($n = 1390$) and urban Tanzania ($n = 2048$) were sampled. Three infants in Kenya were excluded because of severe acute malnutrition. General characteristics of all participants at inclusion are shown in Table 1. HAZ and WAZ in SAC were lower at the rural site in Kenya compared to the urban site in Tanzania ($p = 0.014$ and $p < 0.0001$, respectively). The BMI of non-pregnant women was also lower at the rural site compared to the urban site ($p < 0.0001$).

Salt iodine and water iodine concentration

The self-reported household iodized salt use was 71% in Kenya and 84% in Tanzania ($p = 0.91$). The measured median salt iodine concentration was 43 mg/kg (IQR = 32–54 mg/kg; $n = 195$) in Kenya and 44 mg/kg (IQR = 35–53 mg/kg; $n = 274$) in Tanzania ($p = 0.91$): 44% (total $n = 195$) of salt samples in Kenya and 32% (total $n = 274$) in Tanzania were adequately iodized (15–40 mg/kg). Two samples from Tanzania contained no iodine (<5 mg/kg). From the remaining samples, 0.5% of samples in Kenya and 2% in Tanzania were below recommended levels (<15 mg/kg); 55% and 56% of the samples contained >40 mg/kg, respectively.

In Kenya, household water brought by SAC–WRA pairs ($n = 177$) was generally low in iodine, with 47% of samples measuring 0 μg/L. Yet, 14% of samples measured >10 μg/L, and one sample from a natural spring measured 2943 μg/L (a possible contamination). The mean ± SD iodine concentration in these samples was 20 ± 221 μg/L, and the median was 1 μg/L (IQR = 0–4 μg/L). Samples originated from harvested rain water ($n = 1$), bore holes ($n = 1$), river water ($n = 5$), wells ($n = 1$), springs ($n = 23$), and piped water outlets ($n = 46$). In Tanzania, household water samples ($n = 114$) collected from subsets of students from each of the four schools ranged from

TABLE 1. GENERAL CHARACTERISTICS BY STUDY SITE AND POPULATION GROUP

		Age (years/months)[a]	% Male	Head circumference (cm)	Height/length (cm)	Weight (kg)	BMI	WAZ	HAZ
	n								
Kibwezi District, Kenya									
SAC	291	8.5±1.7[b]	49	51.0 (49.8–52.1)	122.2[c] (115.3–128.5)	20.9[d] (18.5–24.1)	—	−1.4[g] (−2.0 to −0.8)	−1.1[e] (−1.8 to −0.5)
WRA	299	33.0±6.4	—	—	156.6[b] (152.5–161.9)	56.7[b] (49.0–66.8)	23.1[g] (19.7–27.1)	—	—
PW	167	25.3±5.8[b]	—	—	157.9[b] (154.0–161.9)	59.8[b] (52.9–67.5)	—	—	—
LW	149	24.9±5.6[d]	—	—	158.7[b] (153.9–161.5)	55.9[b] (49.7–63.2)	22.5[g] (20.0–25.7)	—	—
BFI	149	3.3±1.5[d]	43	41.0[g] (39.1–42.2)	60.0[c] (56.2–63.5)	6.2[d] (5.4–7.2)	—	0.0[f] (−0.5 to 0.9)	−0.4 (−1.12 to 0.3)
WI	335	11.0±3.9[b]	55	45.1[e] (43.8–46.2)	70.6 (67.9–74.9)	8.3 (7.5–9.3)	—	−0.7 (−1.4 to 0.2)	−0.8[e] (−1.8 to 0.0)
Kinondoni District, Tanzania									
SAC	328	8.7±1.8	46	51 (50.0–52.0)	124.7 (118.3–132.9)	23.8 (20.5–28.5)	—	−0.8 (−1.6, to −0.3)	−0.9 (−1.7 to −0.2)
WRA	329	33.8±6.2	—	—	156 (152.4–160.0)	65.6 (55.1–76.4)	26.7 (22.8–30.9)	—	—
PW	337	26.8±6.0	—	—	156.4 (152.2–160.8)	63.4 (56.5–73.1)	—	—	—
LW	370	27.1±5.3	—	—	156.1 (152.2–160.1)	61.0 (53.1–69.0)	24.9 (21.9–28.3)	—	—
BFI	355	2.4±1.2	46	39.5 (38.0–41.2)	58.3 (55.7–61.2)	5.8 (5.0–6.6)	—	−0.1 (−0.8 to 0.6)	−0.1 (−0.8 to 0.6)
WI	329	10.4±3.5	55	44.6 (43.5–46.0)	71 (68.1–74.0)	8.4 (7.5–9.3)	—	−0.8 (−1.7 to 0.2)	−0.8 (−1.7 to 0.0)

Values are mean ± SD or median (IQR).
[a]Age given is in months for BFI and WI.
Differences between countries are indicated by superscript letters: [b]$p < 0.05$; [c]$p < 0.001$; [d]$p < 0.0001$ (paired independent samples t-test, for normal or log-transformed-normal data); [e]$p < 0.05$; [f]$p < 0.001$; [g]$p < 0.0001$ (Kruskal–Wallis test with Bonferroni correction for nonparametric data).
BFI, breast-feeding infant; BMI, body mass index; HAZ, height-for-age Z-score; IQR, interquartile range; LW, lactating women; PW, pregnant women; SAC, school-age children; SD, standard deviation; WI, weaning infant; WAZ, weight-for-age Z-score; WRA, women of reproductive age.

0 to 596 μg/L. The mean $\pm$ SD iodine concentration from Tanzania was 24 ± 78 μg/L; the median was 4 μg/L (IQR = 0–11 μg/L). There was no difference in the water iodine concentration between the Tanzanian water samples and the Kenyan household water samples ($p = 0.179$, excluding the potentially contaminated sample). The iodine concentration in the Kenya groundwater samples ranged from 3 to 717 μg/L, with a mean $\pm$ SD water iodine concentration of 228 ± 159 μg/L in the bore holes ($n = 23$), 224 μg/L in the wells ($n = 2$), 20 ± 2 μg/L in the springs ($n = 4$), 107 μg/L in the river ($n = 1$), and 7 ± 3 μg/L ($n = 4$) in water from piped outlets (Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/thy).

Urinary iodine, estimated iodine intake, and BMIC

The median UIC was well above the thresholds for adequate iodine nutrition in all population groups and exceeded the threshold for excess iodine intake (≥ 300 μg/L) in SAC but not in PW (Fig. 1). Estimated iodine intake is described in Table 2. The UIC of the SAC or WRA was not significantly correlated with salt iodine concentration or with the household or collected water iodine concentrations in any country.

The median UIC in lactating women was 245 μg/L (IQR = 279–886 μg/L) in Kenya and 192 μg/L (IQR = 120–297 μg/L) in Tanzania ($p = 0.003$), significantly lower than the median UIC in WRA for both study sites ($p < 0.001$; Fig. 1). The median BMIC for lactating women in Kenya was 240 μg/L (IQR = 173–347 μg/L; $n = 126$), and positively correlated with their UIC as well as the UIC of their breastfed infants ($p < 0.01$).

Thyroid function

In Kenya, the median DBS-Tg of of SAC was 37 μg/L (IQR = 25–53 μg/L), and in Tanzania, it was 32 μg/L (IQR = 22–45 μg/L; $p = 0.001$): 46% and 31% of children had elevated DBS-Tg concentrations, respectively (Table 2). The prevalence of elevated DBS-Tg concentrations in PW was approximately half that of SAC: 20% in Kenya and 16% in Tanzania (Table 2). Gestational week was negatively correlated with UIC in Kenyan women ($p < 0.05$) and positively correlated with DBS-Tg in Kenya ($p < 0.05$) and Tanzania ($p < 0.01$). Median DBS-Tg values were >50 μg/L in both breast-feeding infants and weaning infants in both countries.

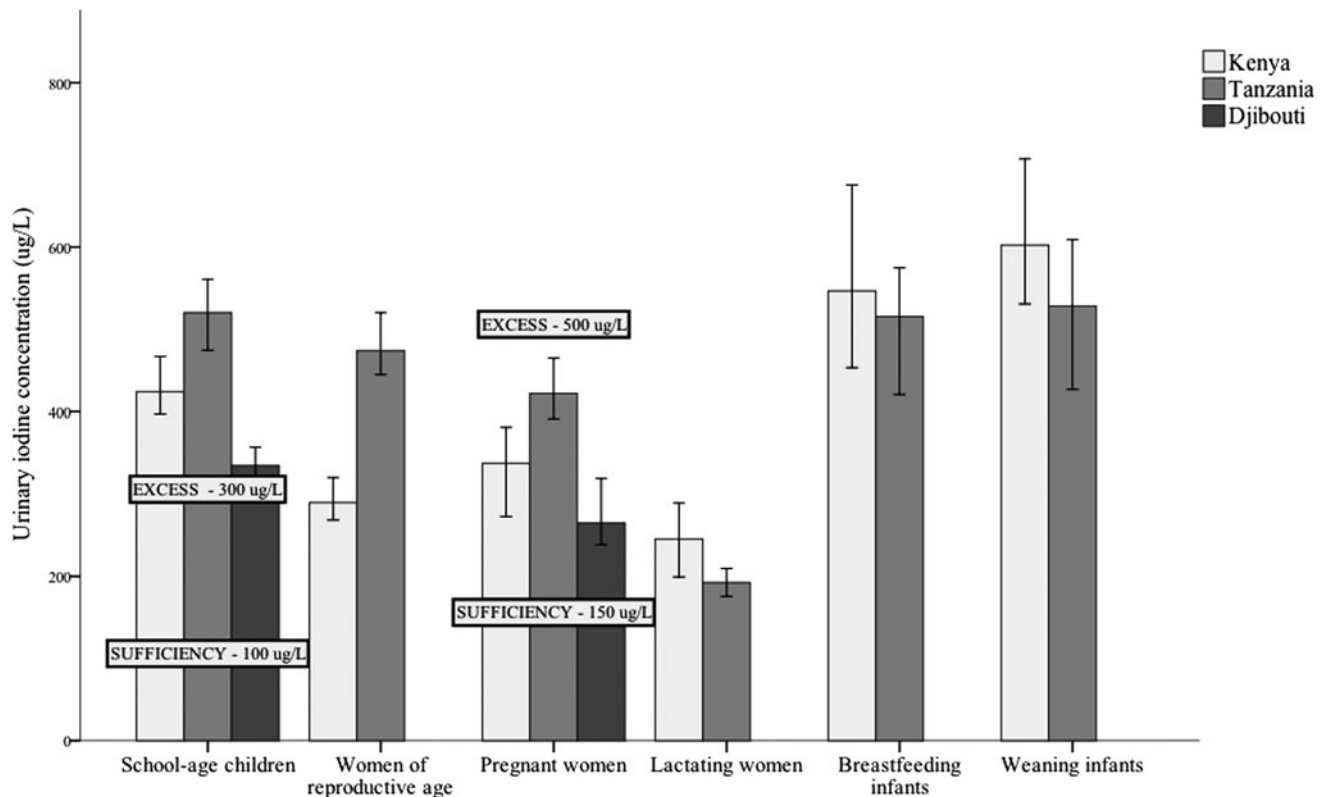The median (IQR) thyroid hormone concentration (DBS-TSH, DBS-TT4) and the prevalence of subclinical and

FIG. 1. Urinary iodine concentration (μg/L) by study site and population group. Error bars denote confidence intervals (CI) based on 1000 bootstrapped samples. Population iodine sufficiency and excess in school-age children are defined by a median urinary iodine concentration of ≥ 100 μg/L and ≥ 300 μg/L, respectively, and, in pregnant women, of ≥ 150 μg/L and ≥ 500 μg/L, respectively (4). Differences within population groups between countries are as follows (Kruskall–Wallis test with Bonferroni correction). School-age children: Kenya–Tanzania, $p = 0.010$; Kenya–Djibouti, $p < 0.001$; Tanzania–Djibouti, $p < 0.001$; women of reproductive age: $p < 0.001$; pregnant women: Kenya–Tanzania, $p = 0.005$; Kenya–Djibouti, $p = 0.026$; Tanzania–Djibouti, $p < 0.001$; lactating women: $p = 0.003$; breast-feeding infants: $p = 0.185$; and weaning infants: $p = 0.009$. Median breastmilk iodine concentration for lactating women in Kenya: 240 μg/L (interquartile range = 173–347 μg/L; $n = 126$).

TABLE 2. MEDIAN UIC, ESTIMATED IODINE INTAKE, AND MEDIAN DBS-TG BY STUDY SITE AND POPULATION GROUP

		n^a	UIC (mg/L)	Estimated median iodine intake (µg/day)	n	DBS-Tg (mg/L)	% Elevated DBS-Tg
Kibwezi District, Kenya	SAC	284	424[c] (294–598)	382	253	37.4[d] (25.0–53.0)	46.2
	WRA	293	289[e] (173–458)	390	213	26.6[e] (18.9–39.8)	—
	PW	162	337[c] (198–505)	546	149	28.1 (19.3–41.3)	20.1
	LW	146	245[c] (279–886)	NA	147	21.5 (15.0–31.1)	—
	BFI	110	546 (323–940)	246	142	51.1[c] (37.8–64.2)	—
	WI	250	602[c] (348–1205)	271	312	56.1[c] (43.4–74.5)	—
Kinondoni District, Tanzania	SAC	317	520 (329–760)	468	310	32.1 (21.7–44.8)	31
	WRA	298	473 (321–689)	639	321	18.1 (12.1–28.8)	—
	PW	330	422 (270–609)	684	335	25.9 (18.1–36.3)	16.1
	LW	363	192 (120–297)	NA	366	19.2 (13.9–27.5)	—
	BFI	208	515 (279–886)	232	341	59.4 (39.8–81.7)	—
	WI	240	528 (255–952)	238	236	52.2 (35.7–77.4)	—
Djibouti	SAC	985	334 (126–493)	301		NA	
	PW	213	264 (168–449)	357			

Data are expressed as median (IQR).
[a]Disparity in sample numbers is due to inability to give sample, inadequate sample, sample loss, or sample deterioration.
[b]Elevated UIC defined as >300 µg/L in SAC and >500 µg/L in PW (5); elevated DBS-Tg >40 µg/L in SAC and 43.5 µg/L in PW (2,29). No thresholds have been defined for other groups.
Differences between groups are indicated by superscript letters: [c]$p < 0.05$; [d]$p < 0.001$; [e]$p < 0.0001$ (paired independent samples t-test, for normal or log-transformed-normal data). Daily iodine intake is estimated using UIC for each population group (except for lactating women) using average urine volumes of 1 L for SAC, 1.5 L for women of reproductive age, 1.8 L for PW (60), and 500 mL for both infant groups (61). Iodine excretion was set at 90% (60).
DBS, dried blood spot; NA, not measured; Tg, thyroglobulin; UIC, urinary iodine concentration.

clinical thyroid disorders are presented by country and population group in Table 3. The prevalence of subclinical and overt hypothyroidism and hyperthyroidism was low in all population groups, except for subclinical hyperthyroidism in WRA (5% in Kenya and 12% in Tanzania; $p < 0.05$) and hypothyroxinemia in PW (10% in Kenya and 15% in Tanzania; $p > 0.05$). The prevalence of hypothyroxinemia increased with trimester in both countries ($p > 0.05$).

DBS-Tg correlated with DBS-TSH in SAC ($p < 0.0001$) and PW ($p = 0.001$) in Kenya, and in SAC ($p = 0.001$), PW ($p < 0.001$), breast-feeding infants ($p = 0.002$), and weaning infants ($p = 0.002$) in Tanzania. DBS-Tg correlated with DBS-TT4 in WRA ($p < 0.001$), PW ($p = 0.009$), and lactating women ($p = 0.036$) in Kenya, and in WRA ($p = 0.027$) and lactating women ($p = 0.049$) in Tanzania.

There were no differences between prevalence of thyroid function disorders with gestational age at 20 weeks, or between women <36 weeks' gestation and those approaching term.

Results: Djibouti

In Djibouti, 1198 subjects were included: 985 SAC and 213 PW from 17 towns, villages, and settlements across the country.

Salt and water iodine concentration

Only 1.6% of all samples were adequately iodized (15–40 mg/kg). Iodine (≥5 mg/kg) was detected in only 9% of all household salt samples ($n = 1200$). Of these, 82% contained <15 mg/kg and the median of the iodine-containing samples was 10 mg/kg (IQR = 6–13 mg/kg; $n = 104$).

Seventy-seven water samples were collected from 21 water outlets, including traditional and drilled wells, public

fountains, and government-managed pipes in the same locations and additional locations across the country. The median water iodine concentration was 92 µg/L (IQR = 37–158 µg/L); the highest concentration was 647 µg/L. There were no significant differences between water from different types of water source, bedrock type, or distance from the sea.

UIC and estimated iodine intake

The median UIC suggests excessive iodine intake in SAC (median UIC 335 µg/L; IQR = 216–493 µg/L) but was within the normal range in PW (median UIC 265 µg/L IQR = 168–449 µg/L; Table 2). The median UIC for SAC and PW was significantly lower than the median UIC in both Kenya and Tanzania ($p < 0.001$). The estimated iodine intake was 301 µg/day and 357 µg/day in SAC and PW, respectively (Table 2).

There were no significant correlations between water iodine concentration and UIC in either group. Similarly, there were no significant trends between UIC and distance from the coast or rock type.

Discussion

The results suggest an iodine intake level well above requirements in all population groups at the study sites in Kenya, Tanzania, and nationally in Djibouti, with the median UIC in SAC exceeding the WHO threshold for iodine excess of 300 µg/L (4) at each study site.

Iodine deficiency was historically endemic in Kenya and Tanzania, but both countries have had USI programs in place for >20 years. Salt iodine concentrations measured in this study suggest high coverage of iodized salt in both study sites, but more than half of the salt samples were over-iodized (>40 mg/kg). The overall salt iodine concentrations were

TABLE 3. TSH, TOTAL THYROXINE CONCENTRATIONS AND PREVALENCE OF THYROID FUNCTION DISORDERS BY STUDY SITE AND POPULATION GROUP

		n	DBS-TSH (mIU/L)	DBS-TT4 (nmol/L)	Subclinical hypothyroidism (%)	Overt hypothyroidism (%)	Subclinical hyperthyroidism (%)	Overt hyperthyroidism (%)	Isolated hypothyroxinemia (%)
Kibwezi District, Kenya	SAC	252	1.5[c] (1.1–2.0)	103.1[a] (87.7–125.4)	1.4[e,f]	0.3[e,f]	0.0[f]	0.0[e,f]	4.8[e,f]
	WRA	213	0.8[c] (0.6–1.2)	91.9[c] (79.3–105.4)	0.3[e]	0.3[e,f]	4.7[f]	0.3[e,f]	5.7[e]
	PW	149	0.8 (0.6–1.1)	142.4 (111.3–165.2)	0.6	0.0	0.6	0.6	10.2[d]
	LW	147	1.0[a] (0.8–1.4)	86.3[a] (69.0–101.0)	0.0[e]	1.3[e]	0.7[e]	0.0[e]	—
	BFI	142	1.1[b] (0.8–1.5)	125.6[a] (102.2–142.3)	0.0	0.0	0.0	0.0	—
	WI	312	1.1[c] (0.9–1.5)	118.1 (96.7–135.7)	0.5	0.0	0.6	0.0	—
Kinondoni District, Tanzania	SAC	310	1.1 (0.9–1.4)	102.2 (81.0–119.7)	0.6[e,f]	0.6[e,f]	0.6[f]	0.0[e,f]	10.7[e,f]
	WRA	321	0.7 (0.5–1.0)	86.4 (73.0–101.9)	0.9[e,f,g]	0.3[g]	11.9[f]	0.0[e,f,g]	10.3[e,g]
	PW	335	0.8 (0.6–1.0)	132.7 (109.8–161.3)	0.3[e,f]	0.0[e,f]	0.3[f]	0.0[e,f]	14.8[d,e]
	LW	365	0.9 (0.6–1.2)	78.0 (64.0–95.9)	0.0	0.8	2.7	0.5	—
	BFI	339	1.0 (0.7–1.3)	112.6 (96.5–138.7)	0.0[e,f,g]	1.1[g]	0.0[f]	0.0[e,f,g]	—
	WI	227	0.9 (0.7–1.2)	119.0 (98.7–141.6)	0.3	0.3	1.5	0.0	—

Data are expressed as median (IQR) or % prevalence.
Differences between groups are indicated by superscript letters: [a]$p<0.05$; [b]$p<0.001$; [c]$p<0.0001$ (paired independent samples t-test, for normal or log-transformed-normal data).
[d]An increase in prevalence of subclinical hypothyroxinemia with trimester ($p<0.05$; chi-square test based on 1000 bootstrapped samples).
[e,f,g]Subsets of thyroid dysfunction group categories whose proportions are not significantly different at $p<0.05$; no superscript letter per population group line indicates no difference between thyroid dysfunction group categories for that population group.
TSH, thyrotropin; TT4, total thyroxine.

comparable between the two countries, but the UIC in SAC, WRA, and PW were consistently higher in Tanzania than Kenya ($p<0.001$), possibly a reflection of high salt consumption in Tanzania (50), although salt intake was not measured in this study. Moreover, high groundwater iodine concentrations were observed in all three study sites, and for the first time in these countries, it is shown that naturally occurring high water iodine concentrations may also be a major contributor to the overall iodine intake, particularly in Djibouti, and must be considered in national iodine deficiency prevention programs. In 2017, after the completion of this study, Djibouti inaugurated a new water pipeline from Ethiopia to provide the arid country with a guaranteed water supply (51), and iodine intake may concurrently fall.

Elevated Tg concentrations were observed in all population groups in Kenya and Tanzania. Tg has been shown, both *in vitro* and *in vivo*, to be a potent regulator of thyroid function at high iodine intake (52), including suppressed expression of the basolateral sodium–iodine symporter (53) and its counterpart on the apical membrane, pendrin (52). Megalin, an endocytic transporter protein, binds colloidal Tg with a high affinity and facilitates its transcytosis through the thyrocyte, avoiding lysosomal degradation and allowing release into the circulation (54). This mechanism may regulate and prevent the liberation of excessive thyroid hormone under changes in iodine intake and may explain why, in the current populations, Tg is elevated but little thyroid hormone fluctuation was observed. The Tg concentrations were correlated with TSH in most groups. Yet, TSH remained within the reference ranges. TSH is the central regulator of thyroid function and controls the synthesis of Tg and its secretion onto the colloidal surface where iodination takes place (53). An elevated Tg seen in response to increasing iodine intake but coupled with normal TSH suggests that in addition to TSH, Tg may contribute to thyroidal adaptation under extremes of iodine intake and may play a regulatory role in thyroid function. Previous studies suggest Tg is a sensitive marker of iodine status (1–3,14,17,19); the present data also support these findings at excessive iodine intake.

An increased prevalence of thyroid disorders was not observed, except for WRA who were affected by a 5% and 12% prevalence of subclinical hyperthyroidism in Kenya and Tanzania respectively, and isolated maternal hypothyroxinemia ranging from 10% to 15% in PW (Table 3). Subclinical hyperthyroidism was defined by a low TSH concomitant with a TT4 within the reference range, following ATA guidelines (45–48). In the U.S. National Health and Nutrition Examination Survey, 1.8% of participants had a TSH <0.4 mIU/L. However, split racially, the proportions were significantly uneven: 4% of black people compared to 1.4% of white people had a low TSH ($p<0.01$), suggesting that racial differences may have a different set point for normal thyroid function (55). Low TSH concentrations might return to normal spontaneously, but generally about half of all cases with subclinical hyperthyroidism may have an increased risk of developing overt hyperthyroidism over time (56). Hyperthyroidism has been previously observed following iodine repletion in iodine-deficient individuals, and iodine-induced hyperthyroidism (IIH) is a recognized effect following the initiation of salt iodization (57–59). In such areas, the WHO recommends a lowered threshold for iodine excess equivalent to a median UIC of 200 μg/L in SAC (4). In the present study populations,

acute IIH is unlikely due to the high naturally occurring water iodine concentrations and the longevity of the USI programs in both countries.

Excess iodine intake has also been associated with subclinical and overt hypothyroidism following acute iodine excess or in individuals with autoimmune thyroiditis exposed to chronic high iodine intake (9,16), but this association is not confirmed by the current data. A possible explanation may be preservation of thyroid function due to the markedly elevated Tg promoting the adaptive mechanisms, as discussed above.

PW and the developing fetus may be vulnerable to iodine in excess (4,37,60–62), though the implications of iodine excess during pregnancy are poorly understood, and data are conflicting. Maternal hormone supply is critical for fetal development, particularly in the first and second trimesters (63). Supply must cover maternal and fetal needs throughout gestation. The fetal thyroid is formed at gestational week 12, organification possible after week 16–20 (64), and, perhaps most importantly here, the Wolff–Chaikoff effect is not functional until week 36 (65). Despite high iodine intake, PW in this study were overall euthyroid, except for maternal hypothyroxinemia (10% and 15% prevalence in Kenya and Tanzania, respectively), which was positively correlated with trimester ($p < 0.05$). Tg was similarly positively correlated with gestational age, suggesting increased thyroid activity, possibly affecting T4 excretion. Hypothyroxinemia during pregnancy has been linked with adverse birth outcomes, including preterm delivery (66) and possibly irreversible low childhood IQ (67–70). The present finding is in agreement with a recent Chinese study reporting an almost threefold increased risk of hypothyroxinemia in PW with UIC $\geq 500\,\mu g/L$ compared to women with lower intake ($n = 7190$; $p < 0.05$) (3). Iron deficiency, prevalent in both Kenya and Tanzania (24,29), is another risk factor for hypothyroxinemia (69). In infants, the estimated iodine intake exceeded the tolerable upper limits of $200\,\mu g/day$ (37), and the Tg concentration was markedly elevated. Although infants may be particularly vulnerable to excessive iodine intake (7,65,71), no thyroid dysfunction was observed in this study, suggesting that the infant thyroid may adapt to high iodine intake when chronic. However, the longterm consequences of thyroidal stress during infancy are uncertain, and the results conflict with findings elsewhere (10,72,73). Long-term follow-up of infants exposed to excessive iodine intake for long periods is required.

A strength of this study is its comprehensive assessment of iodine and thyroid status in a large sample of six life-stage groups using standardized methods. Iodine intake was estimated using dietary excretion assessed by spot urine samples and an estimated fixed urine volume. Creatinine was not measured, and the study did not correct for hydration status. Despite the large overall sample size of this study, recruitment was slower than expected in Kenya, and the desired number of PW, lactating women, and breast-feeding infants could not be reached within the recruitment period. Other reasons for a lower sample size in these groups include withdrawal following consent. A limitation of the study is that older adults were not included, who are considered at highest risk for subclinical or overt thyroid disease (16). Also, antithyroid antibodies were not measured. Positive titers of thyroid antibodies have been identified as a risk factor for the development of morbidity in genetically susceptible individuals with increasing iodine intake (16,74). Though the questionnaire sur-

veyed general dietary intake of native iodine-rich and iodine-fortified foods, processed or pre-prepared foods containing iodized salt, knowledge and use of iodized salt, and source of household water, this could not be used to quantify dietary intake from dietary sources. Bouillon containing iodized salt was widely available, but its potential contribution together with iodized salt (75) was not measured.

In conclusion, chronic excess iodine intake was observed in three study sites in Eastern Africa. Although Tg concentrations were elevated in all studied population groups, thyroid dysfunction was rare. The data confirm that populations can generally adapt well to high intake of iodine, and the findings are important because potentially vulnerable population groups were examined early in the life cycle. High iodine intake in these areas likely arises from a combination of salt iodine concentrations above recommended levels, excessive salt consumption, and groundwater that is high in iodine. Enforcement of salt iodine standards combined with regular monitoring of iodine status is critical to ensure optimal iodine intake. Monitoring and surveillance should be based primarily on UIC in conjunction with measuring salt iodine concentrations. Where intake is elevated and salt found to be over-iodized, excessive salt iodine concentrations should be adjusted and adapted with respect to the current average daily salt intake and the national salt iodization standard. Drinking water should be considered as a potential route of dietary iodine where intake greatly exceeds those expected from iodized salt.

Author Disclosure Statement

No competing financial interests exist.

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