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Estimation of the Prevalence of Inadequate and Excessive Iodine Intakes in School-Age Children from the Adjusted Distribution of Urinary Iodine Concentrations from Population Surveys[1,2]

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Abstract

Background: The urinary iodine concentration (UIC), a biomarker of iodine intake, is used to assess population iodine status by deriving the median UIC, but this does not quantify the percentage of individuals with habitually deficient or excess iodine intakes. Individuals with a UIC <100 μg/L or ≥300 μg/L are often incorrectly classified as having deficient or excess intakes, but this likely overestimates the true prevalence.

Objective: Our aim was to estimate the prevalence of inadequate and excess iodine intake in children (aged 4–14 y) with the distribution of spot UIC from iodine surveys.

Methods: With the use of data from national iodine studies (Kuwait, Oman, Thailand, and Qatar) and a regional study (China) in children (n = 6117) in which a repeat UIC was obtained in a subsample (n = 1060), we calculated daily iodine intake from spot UICs from the relation between body weight and 24-h urine volume and within-person variation by using the repeat UIC. We also estimated pooled external within-person proportion of total variances by region. We used within-person variance proportions to obtain the prevalence of inadequate or excess usual iodine intake by using the Estimated Average Requirement (EAR)/Tolerable Upper Intake Level (UL) cutoff method.

Results: Median UICs in Kuwait, Oman, China, Thailand, and Qatar were 132, 192, 199, 262, and 333 μg/L, respectively. Internal within-person variance proportions ranged from 25.0% to 80.0%, and pooled regional external estimates ranged from 40.4% to 77.5%. The prevalence of inadequate and excess intakes as defined by the adjusted EAR/UL cutoff method was ∼45–99% lower than those defined by a spot UIC <100 μg/L or ≥300 μg/L ($P < 0.01$).

Conclusions: Applying the EAR/UL cutoff method to iodine intakes from adjusted UIC distributions is a promising approach to estimate the number of individuals with deficient or excess iodine intakes. *J Nutr* doi: 10.3945/jn.115.229005.

Keywords: iodine deficiency, iodine excess, iodine intake, urinary iodine, Estimated Average Requirement, EAR, tolerable upper limit, UL, within-subject variation

Introduction

Because both deficient and excessive iodine intakes can have adverse health consequences (1), it is important to assess habitual iodine intakes in populations. But accurate dietary assessment of iodine intake at the individual level is difficult (2, 3), because day-to-day variation in iodine intake is typically high. In European adults, to capture the within-person variation in dietary iodine intake requires ≥10 assessment d (4). The urinary iodine concentration (UIC)[14] is considered a reliable

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[14] Abbreviations used: EAR, Estimated Average Requirement; ICP-MS, inductively coupled plasma mass spectrometry; IOM, Institute of Medicine; mUIC, median urinary iodine concentration; PPS, probability-proportionate-to-size; UIC, urinary iodine concentration; UL, Tolerable Upper Intake Level.

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biomarker of recent iodine intake in populations at all amounts of habitual iodine intake, because >90% of ingested iodine is excreted in the urine in the subsequent 24–48 h (5). The UIC captures the total iodine intake from all dietary sources. The WHO recommends monitoring of iodine status in populations by measuring UIC in spot samples and deriving the median UIC (mUIC); a mUIC of 100–199 μg/L in school-age children indicates adequate iodine nutrition (5). However, this approach does not provide information on the percentage of the population with deficient or excess intakes. Several equations to estimate daily iodine intake from spot UICs are proposed (6, 7). For children, the US Institute of Medicine (IOM) recommends calculating the daily iodine intake from spot UICs from the relation between body weight and urine volume (7).

Nutrient inadequacy of usual dietary intakes is conventionally assessed by the Estimated Average Requirement (EAR) cutoff method, using the population distribution of intakes; the percentage of individuals with usual intakes below the EAR are at risk of nutrient deficiency, and intake is satisfactory when 97–98% of individuals in the population meet the EAR (8–11). This EAR cutoff method could be applied to the distribution of iodine intakes calculated from UIC distributions (2). However, without accounting for within-person variation, the EAR cutoff method will usually overestimate the prevalence of deficiency (12). Thus, iodine intakes calculated from the UIC distribution need to be adjusted for within-person variation (11, 12). Within-person variation can be calculated if repeat UIC samples from the same individual in a subset of the study population are collected, and its effect on the distribution can then be adjusted statistically to more closely resemble the distribution of habitual intakes (11, 12). The prevalence of iodine deficiency could then be defined as the proportion of the population below the EAR from the adjusted distribution. A similar approach, applied to the upper tail of the UIC distribution, could be used to compare intakes with the Tolerable Upper Intake Level (UL) for iodine (7) to estimate the prevalence of excessive intakes.

However, the collection and measurement of repeat urine samples in large surveys may be cost prohibitive in low-resource settings. When only a single urine sample per subject can be assessed, it would be valuable to have an appropriate external estimate of within-person variability to adjust the distribution of iodine intakes (13). Therefore, our study aims were to use the EAR/UL cutoff method and internal within-person variance to develop a new approach to estimate the prevalence of deficient and excessive iodine intakes from distributions of UIC in school-age children and to estimate external within-person variation that could be used to adjust usual iodine intake distributions derived from UIC surveys when only a single sample is collected per subject.

Methods

We used unpublished data from 4 large representative national studies of school-age children in Kuwait, Oman, Thailand, and Qatar and a large regional survey in China. The ages of children included in these studies were 6–12 y in Kuwait, 6–14 y in Oman, 5–13 y in China and Thailand, and 4–14 y in Qatar. At each site, the parents or guardians of the children gave written informed consent. The investigators at each site were asked to collect repeat urine samples in ≥10% of the subjects. We included these recent surveys in the analysis because the mUICs in these countries indicate a range of population iodine intakes from sufficient (Kuwait, Oman, China) through more-than-adequate (Thailand) to excessive (Qatar), according to WHO criteria that were based on the mUIC (5). The iodine laboratories in all 5 studies participate successfully in the Program to Ensure the Quality of Urinary Iodine Procedures of the US CDC in Atlanta (14).

Kuwait. A nationally representative cross-sectional study of elementary schoolchildren was done in March and April 2014. Subjects were recruited with the use of a 3-stage stratified probability-proportionate-to-size (PPS) cross-sectional random cluster design (5). The sample represented 1.84% of children at this age in Kuwait. Ethical permission for the study was obtained from the Ministry of Health and the Ministry of Education, Kuwait City, Kuwait. Weight and heights were measured with the use of standard anthropometric techniques. A spot urine sample was collected from each child before noon. A second repeat spot urine sample was collected in a random subsample of the children on a nonconsecutive day. All urine samples were frozen and kept at −25°C until analysis. The urine samples were analyzed for iodine in duplicate at the Kuwait Institute for Scientific Research by using inductively coupled plasma mass spectrometry (ICP-MS). In Kuwait, legislation stipulates that all food-grade salt must be fortified with iodine at an amount of 20–40 ppm.

Oman. A nationally representative cross-sectional study of elementary schoolchildren was done in early 2014. Subjects were recruited with the use of a 3-stage stratified PPS cross-sectional random cluster design. From the 1368 schools in the Ministry of Education database, 94 schools were selected for enrollment of 2560 children. Ethical permission for the study was obtained from the Ministry of Health, Muscat, Oman. Weights were measured with the use of standard anthropometric techniques. A spot urine sample was collected from each child before noon. A second repeat spot urine sample was collected in a subsample of the children (all the participating children in 11 schools, evenly distributed across regions) on the consecutive day. All urine samples were kept at 4°C until analysis. The urine samples were analyzed for iodine in duplicate at the iodine laboratory in the National Public Health Institute in Muscat by using a spectrophotometric method (15). Oman produces a small amount of its own food-grade salt, and the legislated iodine fortification amount is 15–40 ppm. Imported salt must also meet this guideline and is usually fortified at 30–40 ppm.

China. The study was performed in 4 primary schools in Xiangfen County of Shanxi province in northern China. Ethical permission was obtained from the Shanxi Institute for Endemic Disease Prevention and Treatment, Shanxi, China. Weight and heights were measured with the use of standard anthropometric techniques. A spot urine sample was collected from each child at the 4 schools before noon. A second repeat spot urine sample was collected in a random subsample of the children on a nonconsecutive day. All urine samples were kept at −25°C until analysis. The urine samples were analyzed for iodine in duplicate at the Shanxi Institute for Endemic Disease Prevention and Treatment for analysis. UICs were measured in duplicate by using a spectrophotometric method (15). Chinese legislation stipulates that all edible salt in this region must be iodized at a fortification amount of 25 (18–33) ppm.

Thailand. A nationally representative cross-sectional study of elementary schoolchildren was done in 2012. Subjects were recruited with the use of a 3-stage stratified PPS cross-sectional random cluster design from 50 schools. Ethical permission for the study was obtained from Mahidol University, Bangkok, Thailand. Weight and heights were measured with the use of standard anthropometric techniques. A spot urine sample was collected from each child before noon. A second repeat spot urine sample was collected in a random subsample of the children from 2 of the regions (in Bangkok/Central and the Southern region) on a nonconsecutive day. All urine samples were kept at −25°C until analysis. The urine samples were analyzed for iodine in duplicate at the iodine laboratory of the Human Nutrition Laboratory of the ETH Zurich, Switzerland, by using a spectrophotometric method (15). Thai legislation stipulates a

TABLE 1 Age, sex ratio, and anthropometric characteristics of the children by country[1]

Country	*n*	Age, y	Male:female, *n:n*	Height, cm	Weight, kg
Kuwait	1841	8.8 ± 1.5^{a}	902:939	129 ± 10.2^{a}	32.3 ± 11.8^{b}
Oman	1813	9.8 ± 2.0^{c}	909:904	NM	31.5 ± 11.3^{a,b}
China	385	7.8 ± 1.6^{d}	185:200	126.7 ± 12.4^{a}	27.5 ± 7.3^{d}
Thailand	1107	9.3 ± 1.8^{b}	542:565	132.1 ± 12.1^{b}	30.9 ± 11.0^{a}
Qatar	971	8.7 ± 1.6^{a}	557:414	135.9 ± 13.1^{c}	34.8 ± 12.8^{c}

[1] Values are means ± SDs. Labeled values in a row without a common superscript letter are significantly different, $P < 0.05$. NM, not measured.

fortification amount of 20–40 ppm in all food-grade salt; iodine is separately added as a fortificant to fish and soy sauce.

Qatar. A nationally representative cross-sectional study of elementary schoolchildren was done in 2014. Subjects were recruited with the use of a 3-stage stratified PPS cross-sectional random cluster design from 49 schools. Ethical permission for the study was obtained from Qatar Supreme Education Council, Doha, Qatar. Weight and heights were measured with the use of standard anthropometric techniques. A spot urine sample was collected from each child before noon. A second repeat spot urine sample was collected in a random subsample of the children on a nonconsecutive day. All urine samples were kept at −25°C until analysis. The urine samples were analyzed for iodine in duplicate at the iodine laboratory of the Tanzanian Food and Nutrition Center, Dar es Salaam, Tanzania, by using a spectrophotometric method (15). All salt in Qatar is imported, and the legislated iodine fortification amount in salt at import is 15–40 ppm.

Data analysis. We used the WHO/UNICEF/International Council for Control of Iodine Deficiency Disorders criteria according to mUIC to classify iodine nutrition in children (5). We used the EAR and UL for iodine established by the US IOM (7). The EARs for iodine for girls and boys aged 4–8 y and 9–13 y are 65 and 73 μg/d, respectively. The ULs for iodine for girls and boys aged 4–8 y and 9–13 y are 300 and 600 μg/d, respectively. In Qatar, 1 child aged 14 y and in Oman 6 children aged 14 y were included in the 9- to 13-y group. We used the following equation

TABLE 2 UICs of the UIC 1 and the UIC 2 and the calculated daily iodine intake from the 2 urine concentrations by country in children aged 4–8 and 9–13 y[1]

	UIC 1, μg/L	UIC 2, μg/L	Iodine intake 1, μg/d	Iodine intake 2, μg/d
Kuwait, *n*	1841	251	1841	251
Median	132^{a}	135^{a}	92^{a}	92^{a}
25th, 75th percentiles	84, 200	92, 213	58, 151	59, 155
Range	3–1351	7–777	2–1365	0–532
<100 μg/L, %	33.5			
≥300 μg/L, %	9.9			
Iodine nutrition	Adequate			
Oman, *n*	1813	204	1813	204
Median	192^{b}	211^{a}	131^{a}	137^{a}
25th, 75th percentiles	122, 285	141, 313	80, 206	84, 214
Range	7–570	26–533	4–810	14–843
<100 μg/L, %	17.9			
≥300 μg/L, %	22.1			
Iodine nutrition	Adequate			
China, *n*	385	118	385	118
Median	198^{a}	195^{a}	129^{a}	121^{a}
25th, 75th percentiles	121, 308	122, 266	74, 196	71, 190
Range	5–1407	23–1478	3–926	14–903
<100 μg/L, %	19.0			
≥300 μg/L, %	26.2			
Iodine nutrition	Adequate			
Thailand, *n*	1107	199	1107	199
Median	261^{b}	281^{a}	170^{b}	200^{a}
25th, 75th percentiles	169, 360	192, 398	109, 265	119, 304
Range	4–1238	5–988	3–1598	3–1080
<100 μg/L, %	10.2			
≥300 μg/L, %	37.9			
Iodine nutrition	More than adequate			
Qatar, *n*	971	288	971	288
Median	333^{b}	360^{a}	253^{a}	268^{a}
25th, 75th percentiles	239, 467	272, 491	163, 392	180, 378
Range	5–1833	39–1641	3–2438	24–1805
<100 μg/L, %	6.4			
≥300 μg/L, %	59.7			
Iodine nutrition	Excessive			

[1] Population iodine nutrition from the WHO classification with the use of the median UIC (5). Within country, for UIC and for iodine intakes separately, labeled medians in a row without a common superscript letter are significantly different, $P < 0.05$. Iodine intake 1, intake derived from UIC 1; Iodine intake 2, intake in children derived from UIC 2; UIC, urinary iodine concentration; UIC 1, first spot UIC; UIC 2, repeat spot UIC.

TABLE 3 Proportion of total variance in iodine intake that corresponds to within-person variability, and the fourth moments of iodine intake, by age group and country in children aged 4–8 and 9–13 y[1]

Age group	Kuwait	Oman	China	Thailand	Qatar
4–8 y					
Variance	0.623	0.613	0.472	0.702	0.250
Fourth moment	4.667	3.354	3.000	3.000	7.500
*n*1	797	567	264	497	426
*n*2	108	107	81	82	145
9–13 y					
Variance	0.522	0.335	0.691	0.800	0.333
Fourth moment	3.000	3.000	3.000	3.058	5.811
*n*1	1044	1246	121	609	545
*n*2	144	97	37	117	143

[1] Age groups correspond to the US DRI groups. Seven children aged 14 y were included in the 9- to 13-y-old group. *n*1, number of participants, *n*2, number of participants with a replicate measurement.

to calculate the daily iodine intake from a spot urine sample as proposed by the US IOM (7):

$$\text{Iodine intake }(\mu\text{g/d}) = \text{UIC }(\mu\text{g/L})/0.92 \cdot (0.0009\ \text{L}\cdot\text{h}^{-1}\cdot\text{kg}^{-1}\cdot 24\ \text{h}\cdot\text{d}^{-1})\cdot\text{weight (kg)} \quad (1)$$

In this equation, 0.92 refers to 92% bioavailability and $0.0009\ \text{L}\cdot\text{h}^{-1}\cdot\text{kg}^{-1}$ refers to excreted urine volume from studies in children (16).

The personal computer version of Software for Intake Distribution Estimation (version 1.0, 2003; available from the Department of Statistics, Iowa State University) and the supporting documentation were used to estimate usual intake distributions (17, 18). Details of the method, also known as the Iowa State University method, are discussed in detail elsewhere (8, 19). An estimate of variance from the subsample in which duplicate urine samples were collected was applied to the entire population. This software produces an empirical estimate of the usual nutrient intake of each EAR/UL age and sex subgroup, estimates adjusted percentiles, and calculates the prevalence of inadequate or excessive intake from the subgroup EAR/UL cutoff method.

We computed 4 pooled within-person proportions of total variance (in the transformed scale) as follows. First, we grouped the 3 Middle East countries (Kuwait, Oman, and Qatar) and obtained pooled estimates of the within-person variances by age group, taking a weighted average of the country-level estimates. Weights were equal to the number of persons in each age group with a replicate measurement. For the 2 Asian countries (China and Thailand) we proceeded in the same way. These pooled within-person variance estimates were then used to obtain country or regional-level prevalence of inadequacy or of excess consumption with the use of only the first measurement for each child to derive the distributions of usual iodine intake.

Data were expressed as means ± SDs or ± SEs, or as medians (IQRs). To test for significant differences in quantities of interest, we chose a nominal *P* value of 0.05 as the significance threshold. However, we performed a large number of comparisons; therefore, we adjusted our *P* values as described below to alleviate the confidence erosion that occurs in multiple testing. We used a linear model with country as an explanatory variable to test whether mean age, height, and weight were different across different studies. To guard against erosion of confidence due to multiple comparisons, we used a Tukey adjustment when comparing means (20). Differences in mUIC and in estimated iodine intake between the first and the second measurements within each country were tested with the use of the Wilcoxon-Mann-Whitney test (21). Finally, we performed simple pairwise *t* tests to determine whether there were significant differences between estimated prevalence of inadequate or excessive iodine intakes within countries when using different variance estimates. Because estimates that were based on data from the same country are not independent, we obtained a naive estimate of the SE of the difference in prevalence that did not account for the positive covariance between 2 prevalence estimates that were based on the same sample. Therefore, the *t* statistics to test for differences in prevalence within the same sample, across methods, are biased downward. To guard against a large number of false discoveries (or false findings of significant differences) we used the method proposed by Benjamini and Hochberg (22) to control the false discovery rate at 5%.

Results

The sex ratio, age, and anthropometric characteristics of the children by country are shown in **Table 1**. In the total sample (*n* = 6117), 50.6% of subjects were boys. The mean age ranged from 7.8 ± 1.6 y in China to 9.8 ± 2.0 y in Oman. Significant differences were found in mean age, height, and weight across most pairs of countries (Table 1), likely because of differences in the age of the children who were included. With the use of the unadjusted UIC data, the mUIC, IQR, and range of UIC of the first and second spot urine collections and the calculated

TABLE 4 Distribution of usual daily iodine intakes by country and age group in children aged 4–8 and 9–13 y[1]

Country	*n*	Usual iodine intake, μg	5th Percentile, μg	25th Percentile, μg	50th Percentile, μg	75th Percentile, μg	95th Percentile, μg
Kuwait							
6–8 y	797	101 ± 2	45 ± 6	71 ± 3	94 ± 2	123 ± 6	178 ± 17
9–12 y	1044	133 ± 2	49 ± 5	84 ± 4	119 ± 3	166 ± 7	267 ± 22
Oman							
6–8 y	567	128 ± 2	59 ± 7	92 ± 5	123 ± 3	157 ± 7	215 ± 16
9–14 y	1246	173 ± 3	56 ± 5	105 ± 4	154 ± 3	220 ± 7	352 ± 20
China							
5–8 y	264	159 ± 6	52 ± 8	92 ± 7	135 ± 6	196 ± 14	352 ± 52
9–13 y	121	168 ± 6	79 ± 18	119 ± 13	157 ± 10	206 ± 20	296 ± 54
Thailand							
5–8 y	497	166 ± 3	83 ± 12	124 ± 7	158 ± 5	200 ± 11	278 ± 32
9–13 y	609	251 ± 3	145 ± 18	197 ± 11	241 ± 6	294 ± 15	390 ± 43
Qatar							
4–8 y	426	256 ± 7	75 ± 9	157 ± 8	230 ± 7	325 ± 13	527 ± 37
9–13 y	545	348 ± 9	115 ± 12	215 ± 9	307 ± 8	432 ± 16	722 ± 55

[1] Values are means ± SEs. Age groups correspond to US DRI groups. Seven children aged 14 y were included in the 9- to 13-y-old group.

unadjusted median, IQR, and range of daily iodine intake by country are shown in **Table 2**. The mUIC in the first measurement was significantly different than the mUIC in the second measurement in Qatar, Oman, and Thailand ($P < 0.04$), whereas median estimated intake differed between the first and the second measurements only among Thai children ($P < 0.01$). In addition, the proportion of children with a UIC <100 μg/L and ≥300 μg/L from the first urine sample and the WHO classification of population iodine status on the basis of the mUIC in the first urine sample are shown (Table 2) (5). According to the WHO classification, Kuwait, Oman, and China with mUICs of 131.6, 191.5, and 198.7 μg/L, respectively, would be classified as having "adequate iodine intakes," Thailand with a mUIC of 261.5 μg/L as having "more-than-adequate" iodine intakes, and Qatar with a mUIC of 333.2 μg/L as having "excessive" iodine intakes.

The estimate of the proportion of total variance in iodine intake that corresponds to within-person variability is shown (**Table 3**), that is, the within- to between-person variance component ratio, by age group [the US DRI age groups of 4–8 y and 9–13 y (7)] and by country. In addition, the fourth moments of the measurement error distribution (the kurtosis of the distribution curve) of iodine intake by age group and country are shown (Table 3). Kurtosis is a measure of the "tailedness" of the probability distribution of iodine intakes; greater kurtosis means more of the variance in iodine intake is the result of infrequent extreme deviations, as opposed to frequent moderately sized deviations. The kurtosis values indicate normal or near-normal distributions of iodine intake in all age groups, except children aged 9–13 y in Qatar and children aged 4–8 y in Kuwait and Qatar. Thai children had the highest proportion of total variance in iodine intake that is due to within-person variability (0.702–0.800), whereas Qatari children had the lowest proportion (0.250–0.333). After adjustment for internal within-person variability shown in Table 3, the distribution (mean and percentiles) of the usual daily iodine intakes (in μg) by age group and country is shown in **Table 4**. The iodine intake distributions are shown for Kuwait, Oman, and China (**Figure** 1A–F) and for Thailand and Qatar (**Figure** 2A–D), extrapolated from the single spot urine sample and after adjustment for within-person variability by age group, compared with the EAR and the UL cutoffs.

The proportion of children with daily iodine intakes below the US DRI EAR and above the US DRI UL are shown by age

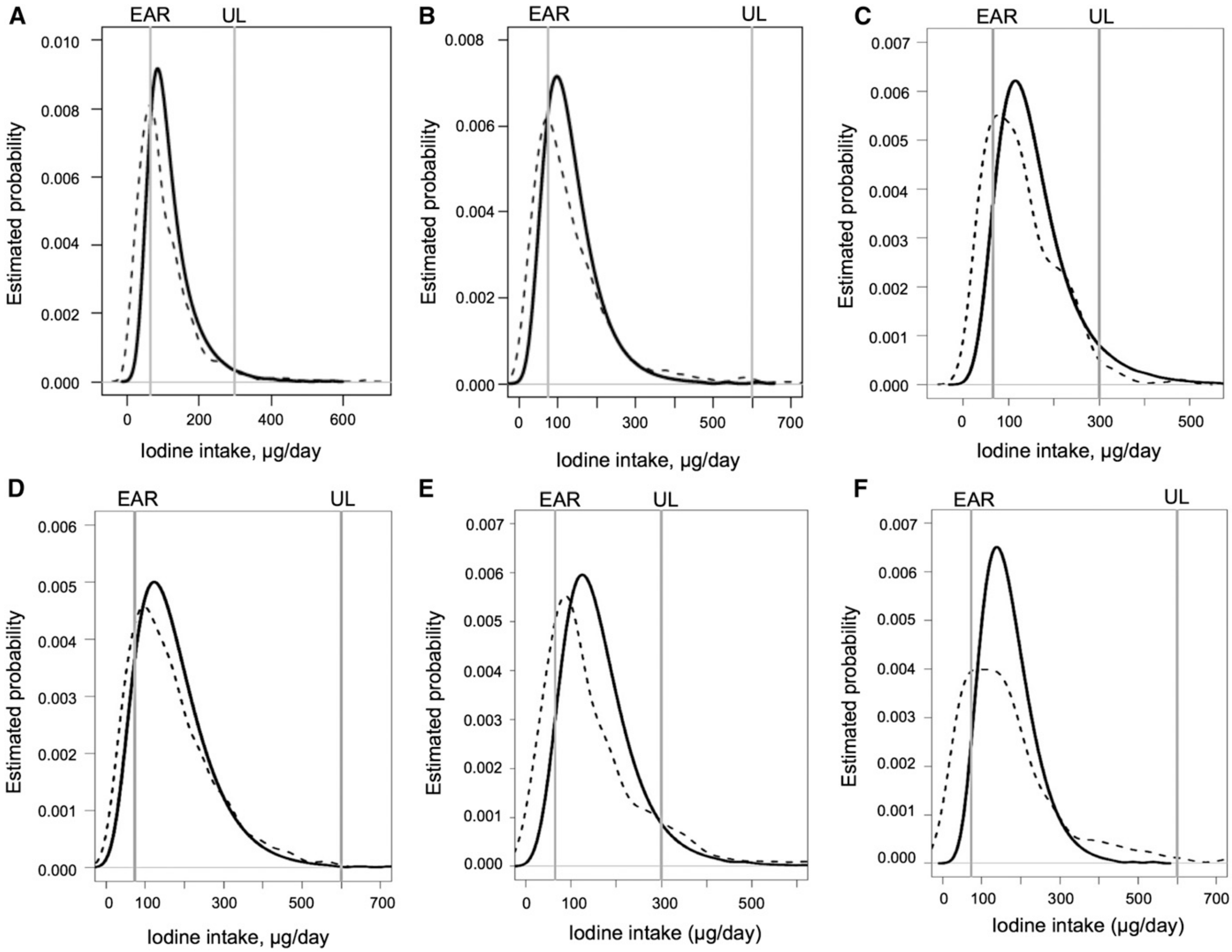

FIGURE 1 The distribution of iodine intake in cross-sectional studies of children aged 4–8 y (A) and 9–13 y (B) in Kuwait (n = 1841), children aged 4–8 y (C) and 9–13 y (D) in Oman (n = 1813), and children aged 4–8 y (E) and 9–13 y (F) in China (n = 385), derived from a single spot urine sample (broken line) and after adjustment for within- and between-subject variation (unbroken line). Age groups correspond to the US DRI groups. Seven children aged 14 y were included in the 9- to 13-y-old group. The vertical gray lines indicate the EAR and the UL by age group. EAR, Estimated Average Requirement; UL, Tolerable Upper Intake Level.

group and country (**Table 5**), *1*) without adjustment, based on a single UIC sample; *2*) after adjustment for internal within-person variance; and *3*) after adjustment with the use of external variance estimates to adjust the usual intake distribution. For the 3 Middle East countries (Kuwait, Oman, and Qatar), the pooled external estimates of the within-person variances by age group were 0.472 and 0.404 for children aged 4–8 y and 9–13 y, respectively. For the 2 Asian countries (China and Thailand) the pooled external estimates of the within-person variances were 0.599 and 0.775 for children aged 5–8 y and 9–13 y, respectively. These pooled within-person variance ratio estimates were then used to obtain country or regional-level prevalence of dietary iodine inadequacy or of excess iodine intake with the use of only the first measurement for each child to derive the distributions of usual iodine intake. With the exception of Qatar, adjustment of the distribution sharply reduces the number of children with intakes below the EAR.

Discussion

The method described in this study to estimate the prevalence of inadequate and excess iodine intakes may be particularly valuable because of the limitations of usual dietary assessments of iodine intake (2, 3). In many countries, the main source of dietary iodine is iodized salt, but FFQs or dietary recalls are typically unable to accurately estimate iodine intake from iodized salt for several reasons (23, 24). First, it is challenging to quantify discretionary household use of salt, whether iodized or not. In industrialized countries most salt comes from processed foods, and, although food tables often specify food salt content, they often do not give the native iodine content of foods, and they seldom specify if the salt used in processed foods is iodized. In addition, the food industry rarely declares whether iodized salt was used in food production, and, even if they do, there may be differences in the amount of iodine among different brands of iodized salt. Finally, day-to-day variation in salt intake is usually large, making it difficult to quantify habitual intake (23, 24). Natural iodine content of other foods, dairy products (25, 26), and drinking water (27) also varies widely, and iodine in food matrices can be accurately measured only by using ICP-MS (25) or other advanced techniques, but only a limited number of laboratories worldwide perform food analysis with ICP-MS.

Currently, surveys of UIC in school-age children are the recommended method to monitor iodine nutrition in populations (5), and the mUIC is a reliable population indicator of iodine status. Unfortunately, the distribution around the mUIC in surveys is often misinterpreted in an attempt to define the number of individuals who are deficient (those with a spot UIC <100 μg/L) or have excess intakes (those with a spot UIC ≥300 μg/L). In 2005 and 2007, WHO defined all children in iodine surveys with a spot UIC <100 μg/L as having low iodine intakes (28, 29). However, dietary iodine intake and, therefore, UIC are highly variable from day to day. In iodine-sufficient countries where most iodine intake comes from iodized salt, UIC (both spot and 24-h urine collections) show an individual day-to-day variation of 30–40% (4, 6, 30). Therefore, in an individual whose average daily iodine intake is adequate to maintain normal thyroidal iodine stores and euthyroidism, iodine intake will show wide daily variation that will result in many individual days when a UIC value will be less than adequate. Thus, even in populations in which iodized salt ensures adequate thyroid stores, there will nearly always be individuals with a UIC <100 μg/L on the day of the survey, but they should not be classified as iodine deficient.

This common error, when applied to UIC distributions from most, but not all, national surveys, greatly overestimates the prevalence of low iodine intakes. This is evident when comparing the percentage of all children with "low iodine intake" (as defined by a spot UIC <100 μg/L, in Table 2) with the percentage with iodine intake below the EAR after adjustment for internal within-person variance (Table 5). Another common error is to classify all children with a spot UIC ≥300 μg/L as having excess intakes. Similarly, this leads to a large overestimation in all countries (Table 5). Adjustment for within-person variance will generally reduce the prevalence of iodine deficiency or excess compared with noncorrected distributions, except in populations with homogeneous iodine intakes or with mean intakes below the EAR or above the UL. In populations with mean intakes below the EAR the distribution is typically skewed to lower intakes, and adjustment may underestimate the prevalence of low iodine intake. In populations with mean intakes above the UL the

TABLE 5 Prevalence of inadequate iodine intake by the EAR and UL cutoff method with the use of internal (''true'') and external (regional) variance estimates to adjust the usual intake distribution in children aged 4–8 and 9–13 y[1]

Age group of children	Unadjusted prevalence below the EAR	True prevalence below the EAR, adjusted with internal variance	Prevalence below the EAR, adjusted with pooled external variance	Unadjusted prevalence above the UL	True prevalence above the UL, adjusted with internal variance	Prevalence above the UL, adjusted with pooled external variance
4–8 y						
Kuwait	35.3 ± 1.7^{a}	19.4 ± 5.7^{b}	25.7 ± 2.5^{b}	2.4 ± 0.5^{a}	0.2 ± 0.4^{b}	0.6 ± 0.4^{b}
Oman	24.3 ± 1.8^{a}	7.5 ± 4.7^{b}	11.7 ± 2.9^{b}	2.7 ± 0.7^{a}	0.2 ± 0.5^{b}	0.8 ± 0.6^{b}
China	20.5 ± 2.5^{a}	$10.1 \pm 4.4^{a,b}$	6.9 ± 4.5^{b}	10.2 ± 1.9	8.2 ± 4.0	5.3 ± 4.0
Thailand	15.3 ± 1.6^{a}	1.4 ± 2.9^{b}	3.4 ± 2.3^{b}	11.1 ± 1.4	3.0 ± 4.8	5.0 ± 2.8
Qatar	3.1 ± 1.5^{a}	$3.8 \pm 1.4^{a,b}$	1.5 ± 1.1^{b}	12.5 ± 2.9^{b}	30.3 ± 2.5^{a}	29.5 ± 4.9^{a}
9–13 y						
Kuwait	30.9 ± 1.4^{a}	17.4 ± 3.6^{b}	21.4 ± 2.1^{b}	0.7 ± 0.2^{a}	0.1 ± 0.1^{b}	$0.2 \pm 0.1^{a,b}$
Oman	18.6 ± 1.1^{a}	10.5 ± 2.1^{b}	9.3 ± 1.6^{b}	0.4 ± 0.2	0.2 ± 0.2	0.1 ± 0.1
China	24.0 ± 3.9^{a}	3.5 ± 7.3^{b}	1.5 ± 4.8^{b}	1.7 ± 1.2	$0.0 \pm \text{ND}$	$0.0 \pm \text{ND}$
Thailand	8.7 ± 1.1^{a}	$0.0 \pm \text{ND}^{b}$	0.1 ± 0.2^{b}	4.6 ± 0.8^{a}	0.1 ± 0.5^{b}	0.1 ± 0.3^{b}
Qatar	2.2 ± 0.8	1.3 ± 0.8	0.9 ± 0.6	7.0 ± 1.2	9.6 ± 2.3	9.4 ± 2.4

[1] Values are means ± SEs. Age groups of children correspond to the US DRI groups. Within country and age group, prevalence estimates below the EAR and above the UL, separately, with a different superscript letter are significantly different, $P < 0.05$. EAR, Estimated Average Requirement; ND = SE not determined; UL, Tolerable Upper Intake Level.

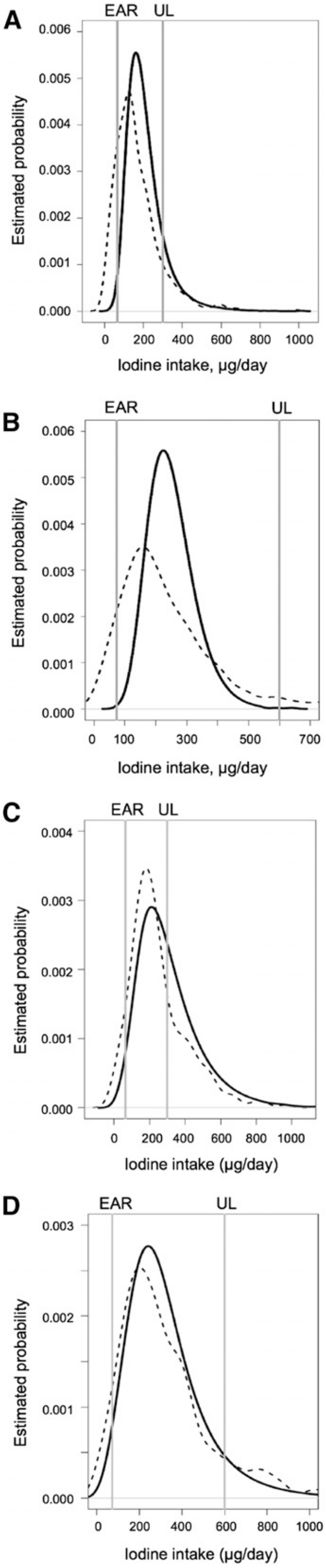

FIGURE 2 The distribution of iodine intake in cross-sectional studies of children aged 4–8 y (A) and 9–13 y (B) in Thailand (*n* = 1107) and children aged 4–8 y (C) and 9–13 y (D) in Qatar (*n* = 971) derived from a single spot urine sample (broken line) and after adjustment for within- and between-subject variation (unbroken line). Age groups correspond to the US DRI groups. Seven children aged 14 y were included in the 9- to 13-y-old group. The vertical gray lines indicate the EAR and the UL by age group. EAR, Estimated Average Requirement; UL, Tolerable Upper Intake Level.

distribution is typically skewed to higher intakes, and adjustment may underestimate the prevalence of excess iodine intake.

In this study, the proportion of total variance in iodine intake that corresponds to within-person variability differed widely among countries and within countries between age groups (Table 3). Differences in the local diet and eating habits, including differences in salt intake, likely contribute to this component of variation in iodine intake. The wide variation in the distribution of usual daily iodine intakes for the different age groups in the countries are shown in Table 4. For example, in Qatar, nearly all dietary iodine comes from imported iodized salt, and the Qatari diet is high in salt, resulting in a high mean daily intake of 255.8 and 348.4 µg/d in the age groups of 4–8 y and 9–13 y, respectively (Table 4). However, the proportion of total variance that was due to within-person variability is only 25.0% and 33.3% in these 2 age groups, respectively, partly because there is greater between-subject variation [as indicated by high kurtosis of the distribution (Figure 2C, D, Table 3)]. In contrast, in Thailand where a wider range of seasoning products contribute to dietary iodine and the staple is rice, the proportion of total variance that was due to within-person variability is 70.2% and 80.0%, but iodine intakes are normally distributed, and there is relatively less between-subject variation in iodine intakes (Figure 2A, B).

One goal of our analysis was to test the hypothesis that external estimates of intraindividual variation could be used to adjust usual intake distributions (13). This would save the costs of a second UIC collection and assay in resource-poor settings. Our data suggest it is preferable to use internal variance estimates to adjust UIC distributions in populations of school-age children, so when possible a repeat sample should be collected and the internal variance estimated. In the case of an iodine survey in which only a single urine sample was collected, as shown in Table 5, with the exception of Qatar, it is always better to use an external estimate of the within- to between-person variance to estimate prevalence of inadequacy than it is to use unadjusted data from a single day of observation. Although results show a similar tendency when we consider proportion of intakes above the UL, we find that fewer of those differences are statistically significant. This is to be expected, given that in almost every case the proportion of intakes exceeding the UL is low and is estimated with a large SE.

The approach described here has several limitations. The relation between body weight and daily urine volume we used was derived from normal-weight United Kingdom children (16). Although recommended by the US IOM (7), the equation has not been validated in children from different countries or in overweight children; thus, the calculation of daily intakes from spot UICs may be imprecise. This equation needs to be validated in other settings around the world. To be able to apply the EAR cutoff approach, the actual prevalence of inadequate intake should be neither extremely high nor low, so this approach may not work for populations with severe iodine deficiency. In addition, the method assumes that estimated usual iodine intakes are independent of estimated requirements and that the distribution of requirements is not skewed (13), but this is likely to be true for iodine. Several different statistical methods to adjust the population distribution of nutrient intake data are proposed; the strengths and weaknesses of the different methods are outlined in earlier reviews (31, 32).

Despite these limitations, applying the EAR cutoff method to iodine intakes derived from UIC distributions may be a promising approach to improve iodine monitoring in populations. Although the mUIC is the recommended measure to interpret overall iodine status, the prevalence of low/high intakes provides important additional information on the proportion of the population at risk of iodine deficiency. It may allow iodized salt program managers to estimate the average increase in daily iodine intake in the population needed to reduce the prevalence of usual iodine intakes below the EAR to <3%, indicating overall adequate iodine intake (9, 10). For example, in Kuwait, the difference between the EAR (by age group, 65 and 73 μg) and the current 2.5th percentiles (by age group, 38 and 41 μg) is the average amount of additional iodine required in the diet of Kuwaiti children to shift the distribution so that only 3% of the population has iodine intakes below the EAR; that is, an additional 27 μg/d for the children aged 5–8 y and an additional 32 μg/d for the children aged 9–13 y. The data from Kuwait, Oman, and China also illustrate that even when the mUIC is >100 μg/L, indicating overall adequate iodine status, a substantial proportion of the population may still have low iodine intakes. The 2 measures may therefore be used complementarily. Conversely, in countries that have high iodine intakes, a similar approach to compare the UL with the current 97.5th percentiles of intake could predict the decrease in dietary iodine that would be needed to achieve a population distribution with only 2–3% above the UL. In addition, by accounting for intraindividual variation, it may reduce the required sample size in UIC surveys to less than the >500 samples now recommended for population assessment (5, 30). Future studies should determine the minimum number of repeat urine samples needed to estimate within-subject variation. Clearly, all of these questions need to be tested in other populations with different iodine status and different diets.

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