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Smoothed Urinary Iodine Percentiles for the US Population and Pregnant Women: National Health and Nutrition Examination Survey, 2001–2010

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Key Words

Urinary iodine · Smoothed percentile · Pregnant women · National Health and Nutrition Examination Survey

Abstract

Background: Iodine intake is essential for normal growth, development and metabolism throughout life, especially for women during gestation and lactation. The present study applies a novel statistical approach, providing smoothed urinary iodine (UI) percentile curves for the total US population as well as the categories of sex, race/ethnicity, women of childbearing age and pregnant women who were participants in the National Health and Nutrition Examination Survey (NHANES) 2001–2010. To our knowledge, this is the first application of this technique to NHANES nutritional biomarker data. ***Methods:*** We used UI and urinary creatinine that were measured in participants aged 6 and older in the NHANES survey periods 2001–2002, 2003–2004, 2005–2006, 2007–2008 and 2009–2010. A nonparametric double-kernel method was applied to smooth percentile curves for UI and creatinine-corrected results. ***Results:*** The UI population estimates showed a U-shaped distribution by age for the total US population. Overall, females had lower UI concentrations and median values compared to males (median UI for females, 141.8 μg/l; median UI for males, 176.1 μg/l; $p < 0.0001$). Non-Hispanic blacks had the lowest median UI concentrations compared to other racial/ethnic groups ($p < 0.0001$). Among women of childbearing age (15–44 years), UI concentrations mostly declined with increasing age. Pregnant women aged 35 years and older tended to have higher UI concentrations than younger pregnant women at similar percentiles. ***Conclusions:*** The smoothed reference distribution of UI concentrations provides an improved and visual display of the entire distribution of values for the US population and specific demographic categories.

Introduction

Iodine is a trace element that is essential for proper thyroid function. When combined with the amino acid tyrosine, iodine produces vital thyroid hormones that control human biochemical reactions, metabolism, enzyme and protein synthesis and are essential to the developing fetal skeletal and central nervous systems [1–4]. Recommended amounts of iodine can be obtained by eating a variety of foods including fish, seaweed, dairy products and products made from grains as well as fruits, vegetables and iodized salt. When iodine intake is inadequate, thyroid enlargement, termed goiter, can result. Historically, endemic goiter, which resulted from iodine deficiency, was described as ‘one of the most important

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and widespread causes of human suffering and of physical and mental degeneracy with which society has had and still has to deal with' [5, 6]. Besides hypothyroidism and goiter, iodine deficiency has been linked to mental retardation and neurodevelopmental disorders in children, mental and physical impairment in adults, increased risk of thyroid cancer and, more recently, a possible link between iodine deficiency and fibrocystic breast disease [4, 7]. Endemic goiter, which historically occurred in geographic areas where iodine is deficient in soil, water and foods, is rarely seen today. However, iodine deficiency still occurs, especially in pregnant women and women of childbearing age. Iodine deficiency has multiple adverse effects on growth and development and is the most common cause of preventable mental retardation in the world [4, 8]. During pregnancy and early infancy, iodine deficiency can cause irreversible effects [4]. Major consequences of insufficient iodine intake are irreversible cognitive and physical impairment and growth failure as a result of prolonged dietary iodine-induced hypothyroidism during pregnancy and lactation, and consequently distressing birth outcomes.

Median (50th percentile) urinary iodine (UI) concentration is useful to assess the iodine status of a population. The World Health Organization (WHO) has defined a population of pregnant women with a median UI concentration of 150 μg/l as evidence of iodine sufficiency, and any iodine concentration below 150 μg/l as evidence of iodine insufficiency [7]. In a combined analysis of National Health and Nutrition Examination Survey (NHANES) 2005–2006 and 2007–2008 data, the median UI concentration for pregnant women was 125.0 μg/l [95% confidence interval (CI) 86.0–198.0 μg/l] [9]. Among these women, 56.9 ± 7.9% had UI concentrations below the WHO cutoff point for iodine sufficiency of 150 μg/l UI for pregnant women [7, 9].

Traditionally, median UI concentrations as well as creatinine-corrected UI and 95% CIs have been used to evaluate the iodine status of populations. In this study, smoothed percentile estimates are presented using the UI data from 5 NHANES survey periods, from 2001 to 2010. The percentile curves are smoothed using a double-kernel nonparametric method, adjusting for NHANES sampling weights and the complex sample design [10]. This method does not make model assumptions and provides smoothed estimates, displaying a continuous illustration of the iodine distribution in the US population. To our knowledge, this is the first time this novel statistical method has been applied to NHANES nutritional biomarker data.

Materials and Methods

We used UI and creatinine data that were measured in a one-third subsample of participants aged 6 and older in NHANES survey periods 2001–2002, 2003–2004, 2005–2006 and 2009–2010, as well as in all survey participants aged 6 and older during the cycle 2007–2008. NHANES, conducted by the Centers for Disease Control and Prevention, is a nationally representative survey and physical examination assessing the health and nutritional status of the civilian, noninstitutionalized US population [11]. The survey consists of an initial in-person interview at the household, followed by a physical examination in a mobile examination center and follow-up questions [11]. We pooled data from the 2001 to 2010 cycles to explore the average estimate for the overall US population as well as subgroups including pregnant women. Pregnant women were oversampled in the NHANES surveys from 2001 to 2006 to achieve more precise estimates involving pregnancy status [12].

During the physical examination, spot urine specimens were collected from participants aged 6 years and older, and aliquots were prepared and stored cold (2–4°C) or frozen until shipped on dry ice to the Centers for Disease Control and Prevention's National Center for Environmental Health, where they were stored frozen (–70°C) for <1 year. UI concentration was measured in a one-third representative sample of the study population, using the inductively coupled plasma mass spectrometry method of Caldwell et al. [13, 14]. The limit of detection for this method was 1.0 μg/l for all 5 survey periods. Urine creatinine was measured in all urine samples using the Jaffé rate reaction performed on a Beckman CX3 Chemistry Analyzer (Beckman Instruments Inc., Brea, Calif., USA).

Self-reported categories of race/ethnicity were non-Hispanic white, non-Hispanic black and all Hispanics, which includes Mexican Americans and other Hispanics. The category 'other' refers to individuals who did not report one of these race/ethnicity groups, and these individuals were excluded from race/ethnicity analyses. Multivitamin, dietary and nutritional supplement information for pregnant participants during NHANES 2001–2008 was obtained in the household interview by asking the following: 'Have you used or taken any vitamins, minerals or other dietary supplements in the past month'. Responses were characterized as 'Yes' or 'No'. These responses were not available for the NHANES 2009–2010 survey period when the paper was prepared.

Using the method of Korn and Graubard [15], median UI measurements (micrograms per liter) and creatinine-corrected UI (micrograms per gram of creatinine) with 95% CIs were estimated for the total US population by age (≥6 years old), sex (male, female) and race/ethnicity groups (non-Hispanic black, non-Hispanic white, all Hispanics) and for women of childbearing age (15–44 years) as well as pregnant women aged 15–44 years. The weighted median test described by Williams [16] was used to compare the median UI measurements between or among different target subpopulations in the NHANES analysis. Statistical analysis was conducted using SAS, version 9.2 (SAS Institute Inc., Cary, N.C., USA), and SUDAAN PROC DESCRIPT, version 10.0 (Research Triangle Institute, Research Triangle Park, N.C., USA).

The nonparametric double-kernel method of Li et al. [10] was used to generate the smoothed percentile curves of UI using uncorrected and creatinine-corrected data. The double-kernel approach is nonparametric so it does not require model assumptions, and therefore a sufficiently large sample size was expected to capture

Table 1. Population-weighted median UI in the US population and subgroups (NHANES 2001–2010)

Category	Median UI, µg/l	Median creatinine-corrected UI, µg/g	Sample size, n
Age			
6+ years (total population)	159.2 (154.7–164.0)	149.3 (144.9–153.6)[1]	18,382 (100.0)
6–11 years	230.0 (214.1–244.8)	263.0 (245.9–280.6)	2,528 (9.0)
12–19 years	179.0 (168.6–188.5)	127.4 (122.11–133.4)[2]	3,833 (12.3)
20–29 years	149.0 (139.7–157.0)	114.8 (107.3–121.4)	2,060 (15.1)
30–39 years	138.4 (130.1–147.0)	119.0 (111.8–126.7)	2,095 (15.1)
40–49 years	140.0 (130.4–146.8)	134.7 (122.0–141.8)	2,036 (16.7)
50–59 years	149.9 (136.7–161.0)	154.9 (145.6–165.2)	1,762 (13.9)
60–69 years	159.1 (143.3–170.4)	183.1 (173.6–194.6)	1,894 (8.8)
70+ years	193.2 (182.6–203.9)	243.7 (229.2–254.4)[3]	2,174 (9.0)
Sex			
Male	176.1 (172.0–182.3)	140.9 (136.0–145.2)	8,981 (48.8)
Female	141.8 (137.8–147.0)	159.2 (153.6–164.4)	9,401 (51.2)
Race/ethnicity			
Non-Hispanic white	163.2 (158.0–168.5)	159.6 (154.9–165.1)	7,678 (72.4)
Non-Hispanic black	138.0 (131.3–145.2)	95.9 (90.9–100.0)	4,252 (12.8)
All Hispanics	170.8 (164.0–176.4)	153.1 (147.5–159.1)	5,613 (14.8)
Females			
All women (15–44 years)	131.1 (123.3–138.0)	123.0 (117.5–129.3)[4]	3,935 (23.4)
Non-Hispanic white	130.6 (116.8–139.0)	129.3 (122.7–136.4)	1,533 (15.9)
Non-Hispanic black	124.0 (117.9–135.0)	84.5 (75.4–89.4)[5]	907 (3.4)
All Hispanics	155.4 (140.0–168.0)	140.0 (133.1–147.2)	1,303 (3.9)
Pregnant women (15–44 years)	145.0 (116.0–182.0)	156.8 (129.4–183.9)	415 (5.9)

Values in parentheses represent 95% CIs or percentages, as appropriate. [1] Sample size for creatinine-corrected UI, 6+ years = 18,378. [2] Sample size for creatinine-corrected UI, 12–19 years = 2,830. [3] Sample size for creatinine-corrected UI, 70+ years = 2,173. [4] Sample size for creatinine-corrected UI, all women 15–44 years = 3,934. [5] Sample size for creatinine-corrected UI, non-Hispanic black women, 15–44 years = 906.

the underlying pattern of the UI distribution. By incorporating survey weights in the curve estimation as well as the bandwidth selections, this approach is a modification of the method described by Yu and Jones [17] and is applicable to large-population survey data such as NHANES. In the curve estimation, percentage UI concentrations are smoothed separately along both the age axis and the UI concentration axis using kernel smoothing and using local linear weighting in the age axis direction. This approach provides robust estimation of the percentile curves of UI by age without making any modeling assumptions. During the bandwidth selection procedure, a bandwidth for the conditional mean is selected first and then modified to obtain the automatic age axis and UI axis bandwidths according to the percentile being estimated. A median correction is conducted to reduce smoothing bias and a bandwidth rescaling procedure to make the bandwidth selection scale invariant [10, 17]. In the analysis, log transformation is first applied to the UI concentration to reduce the right skewness of its distribution, and the resulting percentile estimates are then transformed back to their original scales. QuntlSmoother [18] was applied to generate the smoothed percentiles. This is a statistical software package in language R that estimates quantile smoothers for bivariate data with varying sample weights using the double-kernel method with median correction.

The standard errors for the double-kernel percentile curve can be estimated based on resampling techniques such as bootstrap. As described by Li et al. [10], 200 random half-sample replications are used where one primary sampling unit can be randomly selected from the two (sample) primary sampling units in each (sample) stratum from each survey cycle to form a half-sample replicate. The bandwidth used for the replicate double-kernel estimates is the same as the bandwidth used for the kernel estimates for the original data [19]. The variances can be estimated from these 200 half-sample replicates. Due to the computational intensity, standard error estimation is not included here. In addition, for data with a large sample size (often true in national surveys), the standard error is usually not of concern.

Results

From 2001 to 2010, UI measurements were made in 18,382 participants in NHANES (table 1). Of the 415 pregnant women (5.9% of the women of childbearing age) with measured UI values and of childbearing age,

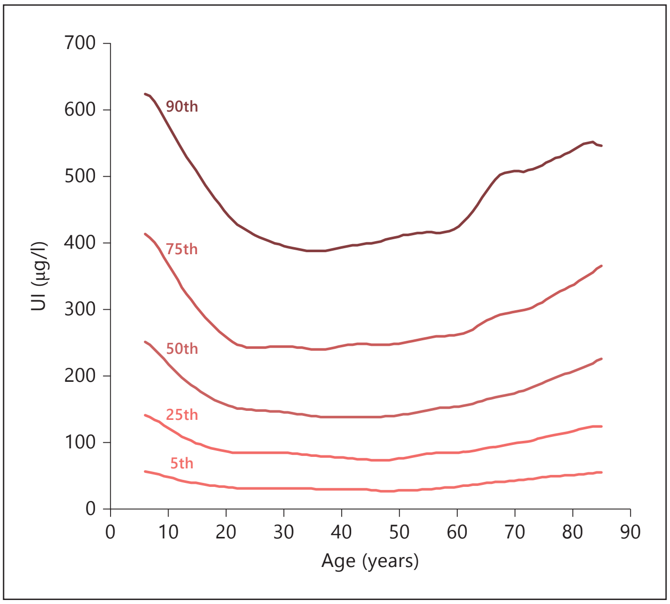

Fig. 1. Selected smoothed UI percentile curves in the US population aged 6 years and older (NHANES 2001–2010).

only 52 (18.87%) were 35 years or older. Table 1 shows the population-weighted results for median UI and creatinine-corrected UI with 95% CIs for the categories of age, sex and race/ethnicity and for women of childbearing age and pregnant women for NHANES 2001–2010. The median UI for the total population 6 years and older was 159.2 µg/l (95% CI 154.7–164.0 µg/l). Males had a higher median UI (176.1 µg/l) than females (141.8 µg/l; $p < 0.0001$). Non-Hispanic blacks had the lowest median UI (138.0 µg/l), followed by non-Hispanic whites (163.2 µg/l) and all Hispanics (170.8 µg/l; $p < 0.0001$). Women of childbearing age had a median UI of 131.0 µg/l (95% CI 130.0–137.8 µg/l), and pregnant women had a median UI of 145.0 µg/l (95% CI 116.0–182.0 µg/l). Both groups of women had a median UI <150 µg/l, the WHO cutoff point for iodine sufficiency in pregnancy [7].

Smoothed percentiles for the total population and demographic categories are presented in figures 1–4 and online supplementary figures 1 and 2 (for all online suppl. material, see www.karger.com/doi/10.1159/000348247). Figures 1 and 2 and online supplementary figure 1 show

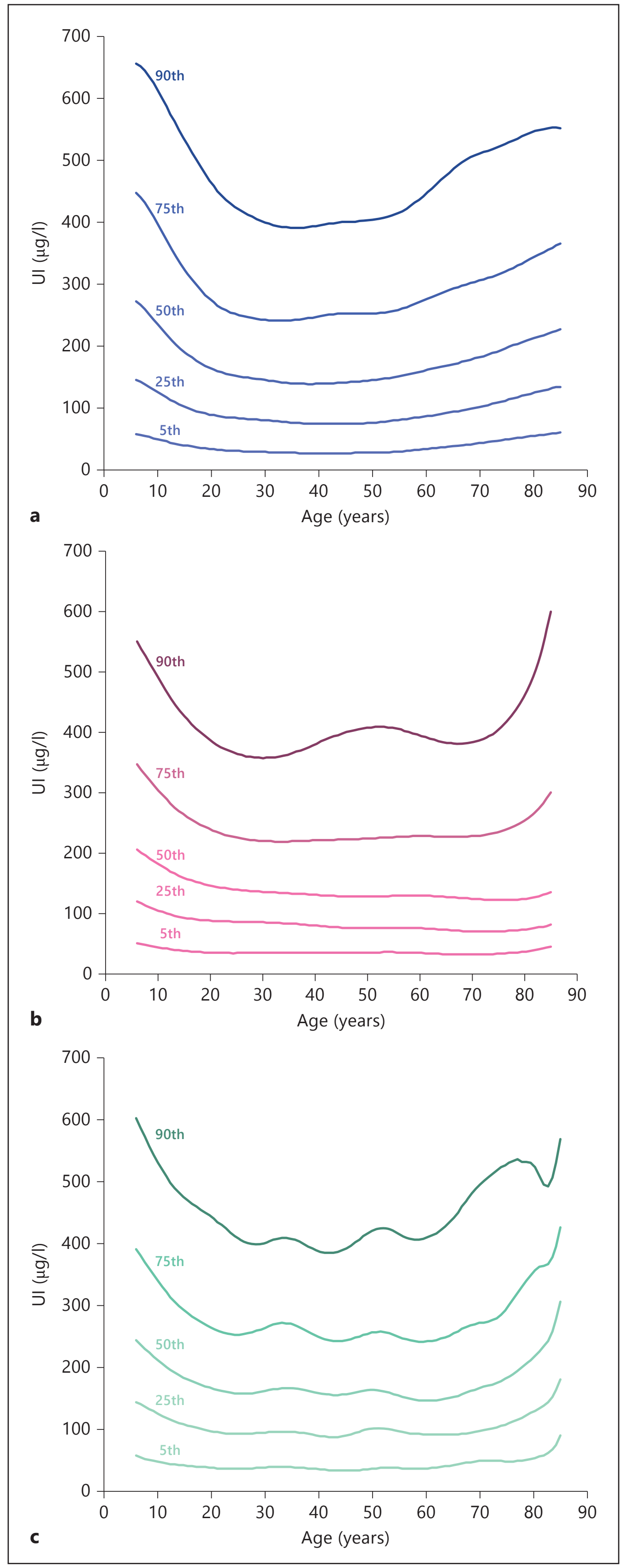

Fig. 2. Selected smoothed UI percentile curves for non-Hispanic whites (**a**), non-Hispanic blacks (**b**) and all Hispanics (**c**) aged 6 years and older (NHANES 2001–2010).

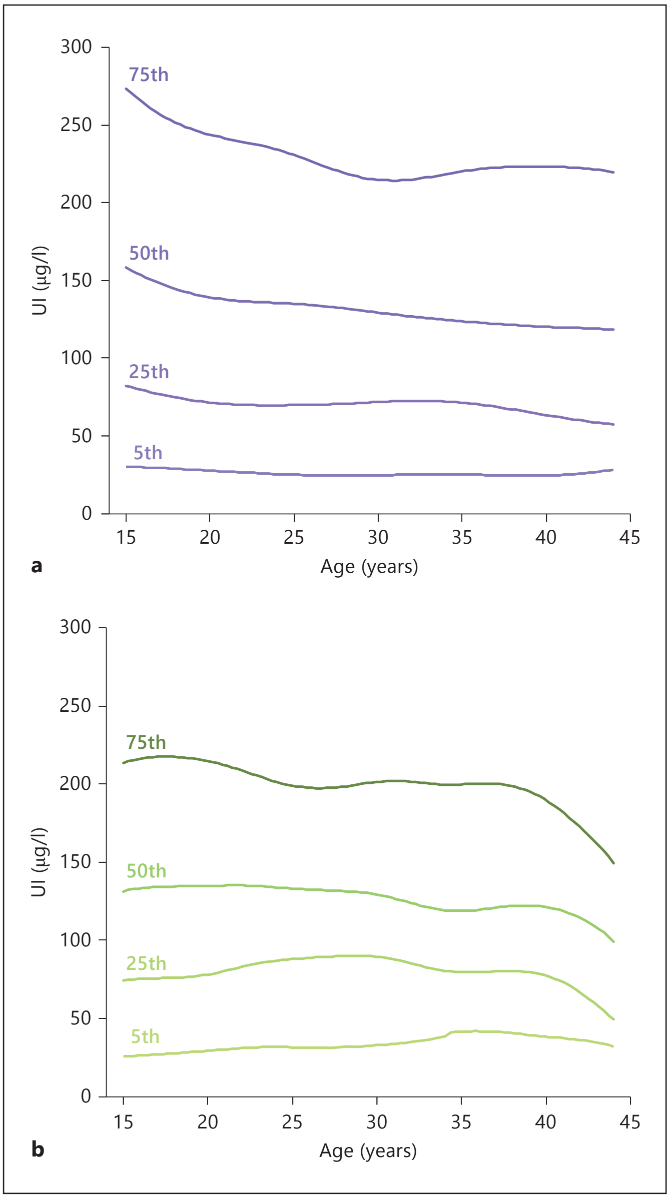

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Fig. 3. Selected smoothed UI percentile curves for women of childbearing age (15–44 years old) (**a**) and non-Hispanic black women of childbearing age (**b**) (NHANES 2001–2010).

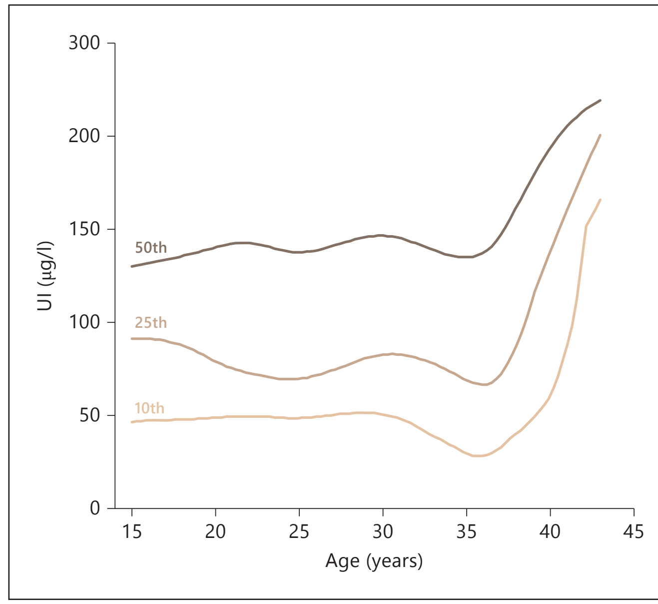

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Fig. 4. Selected smoothed UI percentile curves for pregnant women (15–44 years old; NHANES 2001–2010).

the smoothed estimates for 5th, 25th, 50th, 75th and 90th percentiles of the total population, by sex and by race/ethnicity, respectively. Overall, the UI estimates followed a U-shaped distribution according to age at each of the percentiles (fig. 1). Online supplementary table 1 lists the smoothed estimates of UI for every 5th percentile between the 5th and 95th percentiles for age groups between 6 and 85 years. The median UI estimate for 6–11 year olds was 230.7 μg/l (online suppl. table 1), indicating more than sufficient iodine intake for this age group (UI >200 μg/l). For 12–19 year olds, the median UI estimate was 177.9 μg/l (online suppl. table 1), also indicating sufficient iodine intake for adolescents.

Males had higher UIs at each percentile than females (online suppl. fig. 1a, b). Non-Hispanic blacks had the lowest UIs relative to other racial/ethnic groups at each selected percentile (fig. 2). Interestingly, at the 50th and lower UI percentile for non-Hispanic blacks, there was not an increase in UI at the older ages (50–60 years and above) as observed in other racial/ethnic groups; in fact, the curve was relatively flat (fig. 2).

Figure 3a presents 5th, 25th, 50th and 75th percentiles of UI in women of childbearing age. Most of the UI percentiles from the 25th to the 75th showed a decline in UI with increasing age (fig. 3a; table 2). Smoothed percentiles of non-Hispanic black women of childbearing age showed a similar pattern of decreasing UI as age increased (fig. 3b). Among women of childbearing age, non-Hispanic blacks had the lowest median UI (124.0 μg/l), followed by non-Hispanic whites (130.6 μg/l) and all Hispanics (155.4 μg/l; table 1; $p = 0.001$).

The trend observed in the general population was similar in pregnant women, but UI concentrations were lower. For both groups of ages 15–44 years, the curves appeared relatively flat. Selected smoothed percentiles (10th, 25th and 50th) of pregnant women are presented

Table 2. Smoothed percentiles of UI (μg/l) by age for women of childbearing age (15–44 years old; NHANES 2001–2010)

Age	Selected percentiles										
	25th	30th	35th	40th	45th	50th	55th	60th	65th	70th	75th
15–19 years	93.2	106.4	121.9	137.4	152.9	168.9	185.0	205.7	228.5	254.4	285.8
20–24 years	84.7	97.2	110.4	123.6	137.0	151.8	164.0	181.1	200.1	222.0	248.8
25–29 years	84.3	96.2	108.6	121.0	134.1	147.4	159.5	175.6	193.7	216.3	243.2
30–34 years	82.5	94.2	105.6	116.9	129.6	142.7	156.3	173.0	192.4	216.2	243.0
35–39 years	78.6	90.2	101.5	112.5	124.6	138.3	153.5	171.6	191.2	214.2	240.9
40–44 years	75.4	87.5	99.6	111.6	124.6	138.3	153.4	172.0	193.0	217.2	247.2

Table 3. Smoothed percentiles of UI (μg/l) by age for pregnant women (15–44 years old; NHANES 2001–2010)

Age	Selected percentiles					
	25th	30th	35th	40th	45th	50th
15–19 years	88.7	99.2	111.9	127.8	147.9	133.8
20–24 years	73.4	86.0	99.3	117.6	145.5	140.9
25–29 years	74.7	85.1	97.0	113.1	138.3	141.4
30–34 years	79.4	89.8	101.8	117.9	139.5	141.7
35–39 years	82.0	96.9	111.6	130.5	159.7	152.0
40–44 years	179.5	196.7	217.6	242.4	270.8	211.2

in figure 4 and show the increase in UI that occurs after the age of 35 years. Table 3 shows the smoothed estimates for the 25th–50th UI percentiles of pregnant women. Pregnant women aged 35 years and older had higher UI concentrations than those pregnant women younger than 35 years. The curves for women older than 35 years were unstable because of the small number of UI results (n = 52).

Use of supplements in the past 30 days by all the pregnant women of childbearing age during NHANES 2001–2008 was evaluated using dietary interview data. The analysis was not limited to the subjects who had UI measurements, in order to have sufficient statistical power. From 2001 to 2008, there were 1,030 pregnant women (15–44 years) who responded to supplement use questions during the NHANES interview. Among older pregnant women (35–44 years old), 86.9% took supplements; among younger pregnant women (15–35 years old), 76.6% took supplements. The proportion of older pregnant women taking any supplement was significantly higher than that of younger pregnant women ($p = 0.02$, Rao-Scott F adjusted χ^2 test).

The creatinine-corrected smoothed UI curve for the total population is shown in online supplementary figure 2. Online supplementary table 2 shows the estimates from the 5th to 95th percentiles for creatinine-corrected UI for participants aged 6–85 years. Similar to the uncorrected UI estimates, creatinine-corrected UI estimates were higher for children 6–11 years old and older adults.

Discussion

The double-kernel nonparametric method provides smoothed estimates of selected percentiles by continuous age. The resulting graphical plots provide a continuous visual of population UI results across and between percentiles. The smoothed curve images can supplement specific percentile values and assist with data interpretation. The iodine sufficiency of the US population aged 6 and older and the U-shaped population curve (fig. 1) did not change appreciably over the 10 years of data used in this analysis. Although the double-kernel estimates gave us similar results to the method of Korn and Graubard [15] (online suppl. table 1 compared to table 1), the double-kernel approach produces smoothed percentile curves. Furthermore, the double-kernel method smoothes the data along both the x- and y-axes. The combined methods for data presentation can inform public health decisions and target or prioritize groups for intervention.

The shapes of the smoothed UI curves in the total US population and subgroups using NHANES 2001–2010 data are similar to those reported in previous studies [9, 13, 20]. Children 6–11 years old had a median UI concentration of 230 μg/l, slightly above the cutoff point indicating adequate iodine intake (≥200 μg/l). Overall, non-Hispanic blacks had significantly lower median UI concentrations than either non-Hispanic whites or all Hispanics [9].

The WHO has established population values for UI that correspond to iodine intakes that are adequate, insufficient and deficient [7]. In pregnancy, a median UI of 150–249 μg/l indicates adequate iodine nutrition, and a UI <150 μg/l indicates insufficient iodine [7]. Consequently, women of childbearing age are an important population to monitor for iodine sufficiency. Initiation of iodine supplementation in early pregnancy may be delayed because woman may not be aware of the pregnancy during the early weeks of gestation [9]. Women may not know the importance of iodine in pregnancy and therefore may not know if their iodine intake is adequate. Use of iodized salt has declined with increasing attention to reducing salt consumption. Milk and milk products, an important source of iodine, may be avoided or not tolerated because of lactase deficiency, which is relatively common in the non-Hispanic black population [21]. We found that, in general, the median UI for US women of childbearing age was lower than the WHO cutoff point of 150 μg/l (fig. 3a; table 2). Furthermore, non-Hispanic black and non-Hispanic white women of childbearing age had lower median UIs, with the median UI <150 μg/l, indicating that at least half this population may have inadequate iodine intake. The median UI for all Hispanic women of childbearing age was slightly above 150 μg/l. Consequently, when a non-Hispanic black or non-Hispanic white woman becomes pregnant, her fetus may be at risk from iodine insufficiency and possible neurodevelopmental or skeletal consequences.

Previous NHANES analyses have reported the following median UIs in pregnant women: 173.0 μg/l in 2001–2002; 181.0 μg/l in 2003–2004; 153.0 μg/l in 2001–2006, and 125.0 μg/l in 2005–2008 [4, 9, 20, 22]. Our analysis is more robust, using 5 survey periods of NHANES data (2001–2010) and including a relatively large number of pregnant women because of oversampling in NHANES 2001–2006. Our finding, i.e. a median UI of 145.0 μg/l (95% CI 116.0–182.0 μg/l; table 1) in pregnant women, confirms earlier results and shows that insufficient iodine intake is still prevalent in pregnant women in the US. Of particular concern is the fact that non-Hispanic black women aged 15–44 years have median UIs <150 μg/l at all ages (fig. 3b), indicating iodine insufficiency. Pregnant women younger than 35 years are also of concern, with a median UI <150 μg/l (table 3).

Self-reported supplement use in pregnant women in our analysis was comparable to that reported in NHANES 2001–2006 [22, 23]. Approximately 76.9% of pregnant women stated that they took any supplement in the past 30 days, and about 20.3% of these supplements contained iodine [23]. Other factors contributing to insufficient iodine intake may include use of prenatal supplements lacking iodine, salt avoidance or use of noniodized 'gourmet' and sea salt, consumption of processed foods that use noniodized salt, other factors such as diet and physiologic differences. In summary, based on the smoothed UI percentile curves with data from NHANES 2001–2010, we found that US children and adolescents appeared to have adequate iodine intake, but a majority of non-Hispanic blacks and pregnant women may be at risk for iodine deficiency. The iodine status of pregnant women in the US has been of concern for several years, and in 2006, the Public Health Committee of the American Thyroid Association recommended daily iodine supplementation during pregnancy and lactation in the US and Canada [24]. In 2011, the American Thyroid Association Taskforce on Thyroid Disease during Pregnancy and Postpartum endorsed daily oral iodine supplementation during pregnancy and lactation in North America and included women planning on becoming pregnant in this recommendation [24–26]. With efforts such as these as well as counseling by physicians and health care providers, we anticipate that the median UI for US pregnant women can be improved and reach an adequate iodine intake. Special efforts should be directed at non-Hispanic blacks, particularly females of childbearing age, to increase the median UI concentration.

The technique used in the current study allows for estimating the median and any desired percentiles in a population so that precise and robust estimates of UI concentrations can be made and interventions targeted to groups at greatest risk for insufficient intake.

This will facilitate evaluation of interventions, allow tracking of the iodine status of a population and permit more detailed evaluation of iodine nutrition in a population.

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Disclosure Statement

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. Mention of a product or company name does not constitute endorsement by the Centers for Disease Control and Prevention. None of the authors have conflicts of interest to declare.

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