Iodine Status in Pregnant Women in the National Children's Study and in U.S. Women (15-44 years), NHANES 2005-2010

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention, the National Children's Study or the National Institutes of Health, or the U.S. Department of Health and Human Services.

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Abstract:

Background: This report presents iodine data from NHANES and from a sample of pregnant women in the National Children's Study (NCS) Vanguard Study.

Methods: UI was measured in a one third subsample of NHANES 2005-2006, and 2009-2010 participants and in all 2007-2008 participants age six years and older. These measurements are representative of the general U.S. population. UI was also measured in a convenience sample of 501 pregnant women enrolled in the NCS initial Vanguard Study from seven study sites across the U.S.

Results: NHANES median UI concentration in 2009-2010 (144 µg/L) was significantly lower than in 2007-2008 (164 µg/L). Non-Hispanic blacks had the lowest UI concentrations (131 µg/L) compared to non-Hispanic whites or Hispanics (147 and 148 µg/L, respectively). The median for all pregnant women in NHANES 2005-2010 was less than adequate (129 µg/L), the third trimester women had UI concentrations that were adequate (median UI 172 µg/L). Third trimester women participating in the NCS study similarly had an adequate level of iodine intake, with a median UI concentration of 167 µg/L. Furthermore, NCS median UI concentrations varied by geographic location.

Conclusions: Dairy, but not salt, seafood or grain consumption, was significantly positively associated with median UI concentration in women of childbearing age. Pregnant women in their third trimester in the NHANES 2005-2010 had adequate median UI concentrations, but pregnant women in NHANES who were in their first or second trimesters had median UI concentrations that were less than adequate. Non-Hispanic black pregnant women from both the NHANES 2005-20010 and the NCS consistently had lower UI median concentrations than non-Hispanic whites or Hispanics.

Introduction

Adequate dietary iodine intake is essential to the synthesis of thyroid hormone, which is key for normal growth, development, and metabolism throughout life. Recent data show that 1.88 billion people globally, including 241 million school children, have insufficient dietary iodine intake (1). Iodine deficiency disorders (IDD) are a range of health consequences or abnormalities of the body resulting from a prolonged lack or insufficient intake of iodine, ranging from simple goiter to cretinism, which is a condition of severely stunted physical and mental growth (1, 2). Adequate iodine intake during pregnancy and lactation is especially critical to normal brain development in the fetus (3). While diet-induced hypothyroidism can occur at any stage of life, the most devastating consequences of iodine deficiency occur during fetal development and early childhood, and include miscarriage, stillbirth and congenital abnormalities, and severe and irreversible mental retardation. Iodine deficiency is the leading and most preventable cause of mental retardation in the world (4). The consequence of severe iodine deficiency is a 10–15% reduction in IQ for a population (4).

Strategies to combat the prevalence of IDD focus on ensuring adequate dietary intake. Dairy, grain, seafood, and to a lesser degree, iodized salt are the major sources of iodine in the U.S. (5). However, there is a wide variation in iodine content in foods and iodine content is rarely included in nutritional labeling (5). In the U.S. approximately 60% of iodine consumed comes from dairy products. The iodine is added to dairy products as a consequence of iodine added to cattle feed (6), or use of iodophor disinfectants in the milking process (7, 8). Iodized salt accounts for a small amount of dietary iodine. Approximately 70% of salt consumed in the US comes from processed and restaurant foods which generally do not use iodized salt (9).

The Institute of Medicine has set the Recommended Dietary Allowance (RDA) for iodine in adult men and women at 150 µg per day (10). One teaspoon of iodized table salt contains approximately 400 µg iodine. To support fetal and infant thyroid function, the Institute of Medicine suggests an RDA for pregnant women of 220 µg iodine per day and 290 µg iodine per day during breastfeeding (10). To prevent iodine deficiency, the American Thyroid Association recommends supplementation containing 150 µg of iodine daily for U.S. women of childbearing age during the preconception phase, as well as during pregnancy and lactation (11). In addition, adequate iodine intake before conception (RDA of 150 µg per day) is important to ensure adequate maternal iodine stores to support the fetus. Preconception iodine status of the mother influences the degree of successful maturation of the fetal central nervous system and subsequent neurodevelopment of the child (12).

There are no analytical techniques available to directly measure an individual's daily iodine status. Urinary iodine (UI) reflects iodine intake within the past few days. As a clinical biomarker, UI generally is not useful to classify intake sufficiency or deficiency in a person, but rather to define the risk of a population. UI measurement in 24-h urine collection is preferred, but iodine excretion can be expressed per gram of creatinine in spot urine collections in population groups with very low inter- and intra-individual variation in urinary creatinine (13). The World Health Organization (WHO) defines nutritional iodine sufficiency for a population by UI concentrations as follows: excessive iodine intake, >300 µg/L; more than adequate intake, 200-299 µg/L; adequate intake, 100-199 µg/L; mild iodine deficiency, 50-99 µg/L; moderate iodine deficiency, 20-49 µg/L; and severe iodine deficiency <20 µg/L. The WHO recently defined adequate iodine intake for pregnant women as an iodine excretion of 150-249 µg/L and inadequate iodine intake as represented by iodine excretion <150 µg/L (13).

Given the significant numbers at risk for iodine insufficiency among select population subgroups in the U.S., population-wide monitoring to document UI levels is a necessary public health activity. Recent US population data from NHANES have shown that women and some sub-populations of non-Hispanic blacks tend to have UI concentrations indicating mild iodine deficiency (14). The National Children's Study (NCS) initial Vanguard Study was launched during the same time frame as the 2009-2010 NHANES. The NCS Vanguard Study intent is to provide operational data to inform decisions regarding processes and measures for inclusion in the Main Study. The CDC used samples collected during the Vanguard study to conduct a pilot study. The purpose of the CDC pilot study was to measure a number of environmental chemicals and nutritional biomarkers in the NCS convenience sample of pregnant women from seven study locations throughout the U.S. As part of the CDC pilot study, urine iodine was measured in Vanguard study participants who were in their third trimester of pregnancy. These data help provide a more complete picture of UI status of U.S. pregnant women and enhance the data provided by the NHANES. Our paper will focus on iodine status in the U.S. population as measured by the most recent NHANES 2009-2010 cycle and pregnant women from NHANES 2005-2010 as well as the UI levels for pregnant women who participated in the NCS Vanguard pilot study.

UI has been measured in NHANES since 1971. In recent years, UI has shown a decrease. In all instances where the data is stratified by race/ethnicity, the non-Hispanic black population has had the lowest UI relative to other racial/ethnic groups. Despite oversampling of pregnant women in NHANES 2001-2006, the number of pregnant women participating in the survey is still quite small. The Centers for Disease Control and Prevention (CDC) collaboration with the NCS provided an opportunity to measure UI in a large number of third trimester pregnant women as part of a pilot study to evaluate the clinical biospecimen collection protocols used in the 2009-2010 Vanguard Study. The Division of Laboratory Sciences, National Center for Environmental Health measured UIs and other environmental and nutritional analytes in samples collected from participants enrolled at any of the seven original Vanguard study sites. In this study, results of UI measured in the NCS sample of pregnant women provides additional data on a group at risk for inadequate iodine intake, and will be compared with results from a representative sample of U.S. pregnant women from NHANES.

Data and Methods

NHANES Design

NHANES is conducted by the National Center for Health Statistics (NCHS) of the CDC. It is a program of studies designed to assess the health and nutritional status of adults and children in the United States. The NHANES interview includes demographic, socioeconomic, dietary, and health-related questions. Physical examinations and sample collection for laboratory tests are included. The survey is conducted in two-year cycles. In this report, the NHANES 2009-2010 survey cycle provides the main source of population data for UI. However, we utilized dietary data from NHANES 2007-2008 (dietary data for 2009-2010 were not yet available), and included UI results for pregnant women in NHANES 2005-2010 in order to have a larger sample size. The survey incorporates sample population weights to account for the unequal selection probabilities caused by the cluster design, non-response and planned oversampling of certain subgroups. Pregnant women were oversampled in NHANES 2001-2006. Due to the relatively small number of pregnant women in each two-year cycle for some analyses, we combined UI results for pregnant women from NHANES 2005-2010 for different analyses in this report. For pregnant women ages 15-44 years, UI results from NHANES 2007-2010 were used. For pregnant women ages 15-44 years by trimester, UI results from NHANES 2005-2010 were used. For the entire population, UI results from NHANES 2009-2010 were used. Figure 1 illustrates the combinations of data across several cycles that were used for the projects and a justification for use of different cycles is given.

Data on the sociodemographic variables sex, age, race/ethnicity and pregnancy status were collected. Age was categorized using the following groups: 6-11; 12-19; 20-29; 30-39; 40-49; 50-59; 60-69 and 70 years and older. Race/ethnicity categories were self-reported as non-Hispanic white, non-Hispanic black and Hispanic, which includes Mexican American and other Hispanic. Childbearing age was defined as between 15 and 44 years old. Pregnancy status was determined by a urine pregnancy test. Dairy consumption in the past 30 days was categorized as “never or rare”, “not often” or “often”, where “never or rare” consumption means any dairy product consumed less than once a week in the past 30 days, “not often” denotes some dairy product consumed more than once a week but less than once a day, “often” means dairy product was consumed more than once a day. Salt consumption was determined by response to the question “How often is ordinary salt or seasoned salt added in cooking or preparing foods in your household? Is it never or rarely, occasionally or very often?” Fish or shellfish consumption during the past 30 days was also included for NHANES 2007-2008. Fish includes breaded fish, tuna, bass, catfish, flatfish, haddock, mackerel, perch, pike, pollock, porgy, salmon, sardines, sea bass, swordfish, trout and other fish. Shellfish consists of clams, crabs, crayfish, lobsters, mussels, oyster, scallops, shrimp and other shellfish. Total grain intake was determined based on intake reported on the first day of the dietary interview. Dietary supplement use during the past 30 days was determined by response to the question, “Have you used or taken any vitamins, minerals or other dietary supplements in the past month?”

NCS Design:

NCS is a planned large long-term study of children’s health and development. It examines the effects of the environment, as broadly defined to include factors such as air, water, diet, sound, family dynamics, community and cultural influences, and genetics on the growth, development, and health of children across the United States, following them from before birth until age 21 years. The goal of the study is to improve the health and well-being of children and contribute to understanding the role of various factors on health and disease. Details of the background and organization of this complex undertaking have been described (15, 16). Briefly, the NCS structure consists of the Vanguard Study, Main Study, and formative research that supports and informs the Main Study. The Vanguard Study is a parallel extensive feasibility study that will precede the Main Study to evaluate feasibility, acceptability, and cost of recruitment, logistics, operations, and study visits. The original Vanguard Study began in 2009 and included recruitment of pregnant women at seven selected study locations throughout the U.S. Women were eligible who were not surgically sterile and age 18 through 49 years or currently pregnant. The women had up to two pregnancy visits, which included interviews and collection of biological and environmental samples. Pregnancy visits were scheduled to occur in the first and third trimesters, this study used samples collected from women in their third trimester of pregnancy. Race/ethnicity categories were self-reported as non-Hispanic white, non-Hispanic black and all Hispanic which includes Mexican American and other Hispanic. At the time of this submission, such interview survey results as dietary recall, food intake, and supplement use were not available.

Sample Collection: During the NHANES physical examinations, spot urine specimens were collected into a pre-screened collection cup from participants ages 6 years and older, and aliquots of these specimens were generated and stored cold (2 °to 4 ℃) or frozen until shipped. The samples were shipped on dry ice to CDC's National Center for Environmental Health (NCEH) and were stored frozen (-70 ℃) for <1 year. During the NCS third trimester visits, spot urine specimens were collected from participants into a pre-screened collection cup, frozen and shipped to the NCS Repository (Fisher Bioservices, Rockville, MD) on dry ice, thawed and aliquoted into pre-screened metal-free cryovials, according to NCS protocols, then stored frozen at vapor phase liquid nitrogen temperatures until shipment on dry ice to CDC's NCEH laboratory where they were also stored frozen (-70 ℃) for <1 year.

Iodine Measurements:

In all NHANES cycles except 2007- 2008, UI measurements were obtained for one third of the survey population. For NHANES 2007-2008, UI measurements were obtained for all participants over age five years. Samples were analyzed for UI concentration using the method of Caldwell et al. (17, 18). Briefly, 0.5 mL of urine was diluted 1:10 with 1% (v/v) tetramethylammonium hydroxide, 0.02% Triton X-100™, 25 µg/L tellurium, 5 µg/L bismuth, 5% (v/v) ethanol, 1000 µg/L gold, and 0.5 g/L EDTA. This solution was subsequently analyzed using inductively coupled plasma dynamic reaction cell mass spectrometry. Iodine was quantified based on the peak as a ratio of analyte to internal standard tellurium. The limit of detection was found to be 1.4 µg/L. The LOD as reported is equal to 3*S/N, where S/N is the signal to noise derived from the measurement process as the concentration approaches zero. Four concentration levels of quality controls were analyzed in each analytical batch. Reported results met the accuracy and precision specification of the quality control/quality assurance program of the Division of Laboratory Sciences, NCEH, CDC (19). Two quality control pools were analyzed from 2000 to 2012. One QC pool (n=869) with a concentration of 93 μg/L had a relative standard deviation (RSD) 2.3%. The RSDs for the second pool (n=866) with a concentration of 308 μg/L was 3.0%. Absolute assay accuracy was verified by the blind analysis of two additional iodine reference solutions and the analysis of National Institute of Standard Technology (NIST) 2670A, 2672a and 3668 Standard Reference Materials.

Stability was excellent with no trend observed for the RSD across time. To confirm agreement between survey cycles, 122 previously analyzed urine iodine samples from NHANES study years 2000-2009 were reanalyzed in 2011 by the CDC lab to assure the repeatability of those measurements across time. Concordance correlation coefficient (CCC) (20) was applied to measure the agreement between the measurements of the same iodine sample among different time periods. Overall, the CCC was 0.9955 (95% confidence interval (CI) = 0.9948, 0.9962), which assures the validity of the measurements from instruments across time. The stability of measuring the iodine samples by the instruments across time from 2000 to 2010 at CDC was also established through successful administration and participation in CDC's external quality assurance program: Ensuring the Quality of Urinary Iodine Procedures (EQUIP) (21).

Creatinine measurements

NHANES and NCS urinary creatinine concentrations were determined using the Roche/Hitachi Modular P Chemistry Analyzer (Laboratory Services, L.L.C [Hartford, CT] in 2009-2010 (19). This method is described in Roche's Creatinine plus Product Application # 11775685216V18.

Iodine concentrations were adjusted by using creatinine concentrations to correct for variable urine excretion rates at the time of spot urine specimen collection.

Statistical Analysis

Statistical analyses was conducted using SAS, version 9.2 (SAS Institute, Inc., Cary, NC), and SUDANN PROC DESCRIPT, version 10.0 (Research Triangle Institute, Research Triangle Park, NC). In NHANES, median urinary iodine measurements and the median creatinine corrected UIs with 95% CIs were analyzed based on the method of Korn and Graubard (22). In each NHANES survey period we used sample weights to account for differential nonresponse or no coverage and to adjust for oversampling of some groups. Median test was used to compare the median UIs between or among different target subpopulations in the NHANES analyses (23). Error proportions associated with certain UI thresholds were estimated and were flagged when the relative standard error was greater than 30%. In NHANES, Rao-Scott F adjusted chi-square test was used to test the association between two categorical variables. In NCS, median UI concentrations were analyzed for subpopulations and the Kruskal-Wallis test was applied to test for equality among different study sites. Histogram plots of iodine distribution on pregnant women of childbearing age and pregnant non-Hispanic black women of childbearing age were presented with both NHANES and NCS datasets.

Results

US population NHANES 2009-2010

From NHANES 2009-2010, median UI for the U.S. population six years and older was 144 μg/L (95% CI=132-154) (Table 1), which was significantly lower (p=0.001) than the median of 164 μg/L (95% CI = 154-173) in NHANES 2007-2008 (14). The median UI for all females was 134 μg/L (95% CI = (125-146). Median UI for women of childbearing age (15-44 years) was 124 μg/L (95% CI = 111-139). Median UI for non-Hispanic blacks was 131 μg/L (95% CI = 120-144). Non-Hispanic blacks had significantly lower UIs compared to non-Hispanic whites and all Hispanics (p=0.03) (Table 1). As shown in Figure 2, a U-shaped curve with higher median UI at lower and higher age categories was observed in NHANES 2009-2010. Lowest UI was observed in ages 12-49 years, highest in children ages 6-11 years. The UIs are consistently lower in women of childbearing age compared to the general population, a relationship that has been observed since 2001 (14), Figure 3.

NHANES 2007-2010 US Pregnancy data and NCS

Table 2 presents the median UI with 95% CI in NHANES 2007-2010 by pregnancy status for women of childbearing age (15-44 years) and for NCS pregnant women. The median (95% CI) UI for pregnant women in NHANES 2009-2010 was 135 μg/L (108-172 μg/L) compared to 167 μg/L (151-185) in third trimester pregnant women in the NCS study.

Trimester data NHANES and NCS

Given the limited number of pregnant women in both NHANES 2007-2010 (n=76) or NHANES 2009-2010 (n=22), stratification by trimester was only possible by using all pregnant women who participated in 2005-2010 NHANES (the number of pregnant women was 206 however on 176 participants had trimester data available). Table 3 presents the median UI concentrations for women of childbearing age and pregnant women. Women in their first trimester had a median UI of 109 µg/L (n=42) while the second trimester women had a median UI of 128 µg/L (n=70). The median UI for NAHENS women in their third trimester was 172 µg/L (109-267 (n=64), comparable to the NCS third trimester pregnant women (167 µg/L 95% CI = 151-185 n=501; Table 2).

Distribution of IU in NCS and NHANES (2007-2010)

Among NHANES pregnant women, approximately 55.8% (+ 7.7%) had UI that suggested less than adequate iodine intake (<150 µg/L, Table 2). Among NCS women, approximately 45.3% (+ 2.3%) had UI that indicated less than adequate iodine intake. The distributions of UI for pregnant women in NHANES 2007-2010 and in NCS are presented in Figures 4A and 4B. Figure 4A shows the median UI of 135 µg/L and distribution in pregnant women from NHANES 2007-2010. The 5^{th} and 95^{th} percentiles of the UI distribution were 40 µg/L and 508 µg/L, respectively (Fig. 4A). Figure 4C shows the distribution for NHANES 2007-2010 pregnant non-Hispanic black women. The median UI concentration was 119 µg/L with 5th and 95^{th} percentiles of 34 µg/L and 347 µg/L, respectively. Figures 4B and 4D show the distribution of UI in NCS women. The median UI for all NCS pregnant women was 167 µg/L, with 5th and 95^{th} percentiles of 43 µg/L and 605 µg/L (Figure 4B). For non-Hispanic black NCS pregnant women, median UI was considerably lower (132 µg/L) relative to all NCS pregnant women (Fig. 4D). It is interesting to note that only the NCS population has women with UI concentration greater than ~900 µg/L. These apparent outliers represent only few participants who are taking iodine containing supplements or another significant source of iodine.

Race/Ethnicity 2009-2010 NHANES and NCS

Table 4 provides details on UI concentration by race/ethnicity and age from both 2009-2010 NHANES and NCS. Non-Hispanic blacks in each age category and in both study cohorts had lower median UI concentrations than non-Hispanic white and all Hispanic. The trend is consistent for uncorrected and creatinine corrected data.

Geographic location NCS data only

Table 4 also provides the NCS sample population stratified by geographic locations. The NCS participants consist of pregnant women from seven different geographic locations in the US. The participating study centers were located in California, North Carolina, Minnesota and South Dakota, New York, Pennsylvania, Utah and Wisconsin. Table 3 provides NCS median UI concentrations by the geographic region of the study site. All seven sites have different median UI concentrations. All collection sites used collection material that had been prescreened at the CDC. It is unlikely that protocol or material influenced the results. Urine iodine is very stable once collected as discussed in the "Data and Methods section". Several study sites had median UI concentrations <150 µg/L. The California median UI was 107 µg/L well below those found in North Carolina, South Dakota- Minnesota and Utah (217 µg/L, 205 µg/L and 190 µg/L, respectively). New York and Wisconsin had median UI of 150 µg/L and 145 µg/L, respectively, while Pennsylvania had a median UI of 125 µg/L. Median UI concentrations in California, Pennsylvania and Wisconsin were below the recommended median UI concentration of 150 µg/L for pregnant women.

Dietary questions NHANES 2007-2008

Dairy products consumption has been shown to be significantly associated with iodine intake (6). Table 5 shows the association between dairy consumption in the past 30 days and race/ethnicity for women of childbearing age in NHANES 2007-2008. The proportion of non-Hispanic black women who never or rarely consumed dairy products in the past 30 days was 39.8%, significantly higher than non-Hispanic whites (27.1%) or all Hispanics (31.1%) ($p=0.004$, Rao-Scott F adjusted chi-square test). The median UIs for non-Hispanic blacks was the lowest in each dairy consumption level compared to other race/ethnicity groups.

The relationship between salt consumption and median UI was also evaluated across race/ethnicity categories (Table 5). Hispanics reported greater salt use than the other groups, with 17.2% reporting "Never or Rare use" during the last 30 days compared to 24.5% for non-Hispanic blacks and 27.1 % for non-Hispanic whites. The proportion of Hispanic women who reported using salt "Often" was 55.6 %, significantly higher than non-Hispanic blacks (45.9%) and non-Hispanic whites (35.9%) ($p<0.0001$, Rao-Scott F adjusted chi-square test).

Fish or shellfish intake during the last 30 days was not significantly associated with median UIs in racial/ethnic groups with the exception of Hispanics (Table 5). Hispanic women who reported fish or shellfish intake had significantly higher median UI compared to non-fish consuming Hispanics ($p=0.03$). There was no significant association between higher median UI and grain intake, or supplement use in each race/ethnicity category during the past 30 days (data not shown).

Discussion

NHANES 2009-2010 indicates that median UI in the general population is 144 μg/L (95% CI=132-154). That concentration is significantly lower than in the 2007-2008 cycle, in which median UI was 164.0 μg/L (95% CI= 154-173, p=0.001). In NHANES 2009-2010, certain groups within the U.S. population did not achieve adequate dietary iodine intake. Non-Hispanic blacks had a significantly lower UI concentration than non-Hispanic whites and all Hispanic groups. Non-Hispanic white children had the highest UI levels, in the more than adequate range, while non-Hispanic black and Hispanic children had median UI in the adequate range. In the U.S. population, age groups 12-49 years had the lowest UI, which has been noted before (14). As in previous NHANES survey periods, women had lower UIs than men (14). NHANES data (2007-2010) indicates that 37.3% of non-pregnant women of childbearing age (n=1492) have UI concentrations below 100 μg/L, while 55.8% of pregnant women (n=76) have UI concentrations less than 150 μg/L. Meanwhile, in the convenience sample of 501 pregnant women from the National Children's Study, 45.3% of the participants had UIs less than 150 μg/L. The observed difference in the proportion of pregnant women with UI< 150 μg/L is most likely because the NCS participants were all in their third trimester of pregnancy. While there were only 76 pregnant women in NHANES 2007-2010 with UI measurements, limiting our ability to look at data stratified by trimester of pregnancy due to insufficient power, by combining NHANES 2005-2010 data we were able to increase our sample of pregnant women to 206. We stratified these into trimester groups. The NHANES third trimester UI concentration 172 μg/L (95% CI=109-267) is very similar to the UI concentration found in the third trimester women participating in the NCS pilot study (UI=167 μg/L (95% CI=151-185).

UI levels found in women in the third trimester in both NHANES and NCS were in the adequate iodine intake range. Women in late pregnancy may be more attuned to maintaining adequate nutrition or may be taking supplements with iodine. Most iodine-containing multivitamins should have at least 150 μg iodine, but only about half of the multivitamins sold in the U.S. contain iodine (12). According to Gregory et al. (24), in the National Health and Nutrition Survey (NHANES) 2001-2006, approximately 76.9% of pregnant women reported prenatal supplement use. However, only 20.3% of those preparations contained iodine. Prenatal vitamins are not a dependable source of iodine, since only about 51% may contain iodine and of those that do, the measured iodine concentration can vary ±50% from the labeled content (12). In addition to being an inconsistent source of iodine, relying on the use of prenatal vitamins to ensure iodine sufficiency during pregnancy may miss the very early stages of the fetal development. Not surprisingly, when we looked at supplement use (yes or no) in NHANES women of childbearing age, there was no significant correlation between those using supplements and those not using supplements.

There is a need to look beyond pregnancy status to identify what may be influencing UI concentrations in subpopulations. NHANES 2009-2010 indicates that non-Hispanic blacks had lower UI levels compared to non-Hispanic whites and all Hispanics across all age categories. However, the number of pregnant participants in NHANES is insufficient to look at pregnancy status by race/ethnicity. In the NCS pilot study, non-Hispanic black pregnant women ages 20 years and above had lower UI concentrations than both non-Hispanic whites and Hispanics, which was also lower than what WHO suggested for pregnant women. There were only five

NCS women less than 20 years, and their median UI was 224 μg/L (95% CI=106-1701). There is a wide confidence interval with a very small population.

The NHANES and NCS UI data suggest that non-Hispanic black women have lower UI concentration than other women. Additionally, non-Hispanic black women had lower dairy consumption, based on NHANES 2007-2008 data. Almost 40% of non-Hispanic black women of childbearing age never or only rarely consume dairy products compared to 27.1% of non-Hispanic white women and 31.1% of Hispanics. Moreover, proportionately more Hispanic and non-Hispanic white women of childbearing age reported consuming dairy products daily than do non-Hispanic blacks. Non-Hispanic black women reporting lower rates of dairy consumption is consistent with recent data on U.S. population reports of lactose intolerance (8). That study found that 76% of adults reporting to be lactose intolerant were female, and among females, 50% were non-Hispanic black, 30% non-Hispanic white, and 20% Hispanic. Self-diagnosed lactose intolerance, and consequent avoidance of dairy products may be one of the contributing factors in the racial/ethnic differences we have shown in UI concentration.

Neither salt use during food preparation or grain intake was significantly associated with an increase in median UI for any race/ethnic category of women of childbearing age. However, among women of childbearing age in NHANES who claimed to never or only rarely consume salt, Hispanic women had the highest median UI (154 μg/L) compared to non-Hispanic whites (110 μg/L) or non-Hispanic blacks (117 μg/L). The use of salt, consumption of grain or fish/shellfish intake did not significantly affect UI, although there were racial/ethnic differences in reported salt use and fish/shellfish intakes.

Analysis has shown regional differences in UI among pregnant women in the NCS study. Future work with the NCS may provide the statistical power needed to stratify the participants within each region by race/ethnicity. The present data suggest that race/ethnicity is an important predictor of iodine status. However geographic location may prove to be an equally important predictor. Additionally, within pregnant women in the NCS, we have identified iodine insufficiency among non-Hispanic blacks and among NCS subgroups evaluated geographically. These data enhance ongoing efforts to identify populations at risk for iodine deficiency and may help direct efforts to ensure optimal fetal and postnatal development. NCS will be an important tool to assist in evaluation of U.S. population iodine intake in a vulnerable group. The NCS not only has important data on pregnant women but will collect data that may link the iodine status in pregnant women to birth and child health outcomes.

This study has several strengths. This is the largest known population of pregnant women to be surveyed for UI concentration at one time in the US. Through NHANES and NCS we have a diverse sample set covering different ethnic groups, ages, geographic regions and different stages of pregnancy. There are several limitations. These include the temporality of the UI biomarker, limited personal and health information, and unknown selection biases in the NCS convenience sample.

Conclusion

The median UI concentration for the general U.S. population in NHANES 2009-2010 was significantly lower than the levels found during NHANES 2007-2008. These differences likely result from variations in dietary iodine intake for both the general population and for women of childbearing age. Grain, salt, and fish/shellfish had little effect on UI in women of childbearing age except for Hispanic women, in whom median UI was correlated with fish and shellfish intake. A higher proportion of non-Hispanic black women may avoid dairy products due to concerns about lactose intolerance. Children had a higher UI level than adults. Non-Hispanic white and Hispanic children have UI levels in the upper range of adequate or in the more than adequate range. Non-Hispanic black children have UI concentrations that put them solidly in the adequate range.

NCS data provide a unique look at a large population of pregnant women in the U.S. The data indicate that third trimester pregnant non-Hispanic black women age 20 years and older were the only racial/ethnic group with median UI below 150 μg/L. This racial/ethnic UI pattern was consistent with observations in NHANES data for the general population.

Understanding the median UI differences within subpopulations of the U.S. may help to identify where public health interventions should be focused to ensure adequate iodine nutrition for all, and can allow educational efforts to focus on groups for which evidence indicates inadequate iodine intake. Prevention of unnecessary self-imposed dairy restriction and improved iodine intake may be achieved by medical evaluation and education of individuals who perceive themselves to be lactose intolerant but who are not. Individuals with confirmed lactose intolerance, particularly women who are pregnant or who are of childbearing age, should be counseled about iodine supplementation. Public health intervention may include continued efforts by the medical community and public health officials to promote the use of iodine-containing prenatal vitamins and to promote continued efforts to monitor actual iodine content in prenatal vitamins. The NCS data have provided an opportunity to look across seven geographical locations, noting differences in median values among study sites. Further study is needed to determine if the concentration of iodine in the dairy consumed varies geographically and may be a significant factor in median UIs, along with race/ethnicity.

Disclosure Statement

The authors declare that no competing financial interest exists.

References

1. Andersson M, Karumbunathan V, Zimmermann MB. Global iodine status in 2011 and trends over the past decade. The Journal of nutrition 2012;142:744-50.

2. Hetzel B. Iodine deficiency disorders (idd) and their eradication. The Lancet 1983;322:1126-9.

3. Hetzel BS, Delange F, Dunn JT, Ling J, Mannar V, Pandav C. Towards the global elimination of brain damage due to iodine deficiency. Delhi: Oxford University Press, 2004.

4. Bleichrodt N, Born M. A meta analysis of research on iodine and its relationship to cognitive development. In: Stanbury J, ed. The damaged brain of iodine deficiency, Vol. New York, NY: Cognizant Communication, 1994:187-91.

5. Murray CW, Egan SK, Kim H, Beru N, Bolger PM. Us food and drug administration's total diet study: Dietary intake of perchlorate and iodine. Journal of exposure science & environmental epidemiology 2008;18:571-80.

6. Hemken RW. Milk and meat iodine content - relation to human health. J Am Vet Med Assoc 1980;176:1119-21.

7. Pearce EN, Pino S, He X, Bazrafshan HR, Lee SL, Braverman LE. Sources of dietary iodine: Bread, cows' milk, and infant formula in the boston area. The Journal of clinical endocrinology and metabolism 2004;89:3421-4.

8. Nicklas TA, Qu HY, Hughes SO, He MY, Wagner SE, Foushee HR, Shewchuk RM. Self-perceived lactose intolerance results in lower intakes of calcium and dairy foods and is associated with hypertension and diabetes in adults. Am J Clin Nutr 2011;94:191-8.

9. Dasgupta PK, Liu YN, Dyke JV. Iodine nutrition: Iodine content of iodized salt in the united states (vol 42, pg 1315, 2008). Environ Sci Technol 2008;42:7025-.

10. Medicine Io. Dietary reference intakes for vitamin a, vitamin k, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc.: The National Academies Press., 2001.

11. Public Health Committee of the American Thyroid A, Becker DV, Braverman LE, Delange F, Dunn JT, Franklyn JA, et al. Iodine supplementation for pregnancy and lactation-united states and canada: Recommendations of the american thyroid association. Thyroid 2006;16:949-51.

12. Gregory CO, Serdula MK, Sullivan KM. Use of supplements with and without iodine in women of childbearing age in the united states. Thyroid 2009;19:1019-20.

13. Organization WH. Assessment of iodine deficiency disorders and monitoring their eliminationa guide for programme managers. In: Orginization WH, ed., Vol. Third Edition. ed, 2008.

14. Caldwell KL, Makhmudov A, Ely E, Jones RL, Wang RY. Iodine status of the u.S. Population, national health and nutrition examination survey, 2005-2006 and 2007-2008. Thyroid 2011;21:419-27.

15. Mortensen M, Hirschfeld S. The national children's study: An opportunity for medical toxicology. Journal of Medical Toxicology 2012;8:160-5.

16. The national childrens study. http://www.nationalchildrensstudy.gov/Pages/default.aspx (Accessed 8/3/2012.

17. Caldwell KL, Jones R, Hollowell JG. Urinary iodine concentration: United states national health and nutrition examination survey 2001-2002. Thyroid 2005;15:692-9.

18. Caldwell KL, Maxwell CB, Makhmudov A, Pino S, Braverman LE, Jones RL, Hollowell JG. Use of inductively coupled plasma mass spectrometry to measure urinary iodine in nhanes 2000: Comparison with previous method. Clin Chem 2003;49:1019-21.

19. Caudill SP, Schleicher RL, Pirkle JL. Multi-rule quality control for the age-related eye disease study. Statistics in medicine 2008;27:4094-106.

20. **Lin LI. A concordance correlation coefficient to evaluate reproducibility. Biometrics 1989;45:255-68.**

21. **Ensuring the quality of urinary iodine procedures. http://www.cdc.gov/labstandards/equip.html (Accessed Auguest 3 2012).**

22. **Korn EL, Graubard BI. Confidence intervals for proportions with small expected number of positive counts estimated from survey data. Survey Methodology 1998;24:193.**

23. **Williams RL, Perritt RL. The weighted median test for finite population samples. Washinton, DC: American Statistical Association., 1986.**

Figure 1. Description of NHANES and NCS population utilized for each of the different analyses in this investigation and the justification.

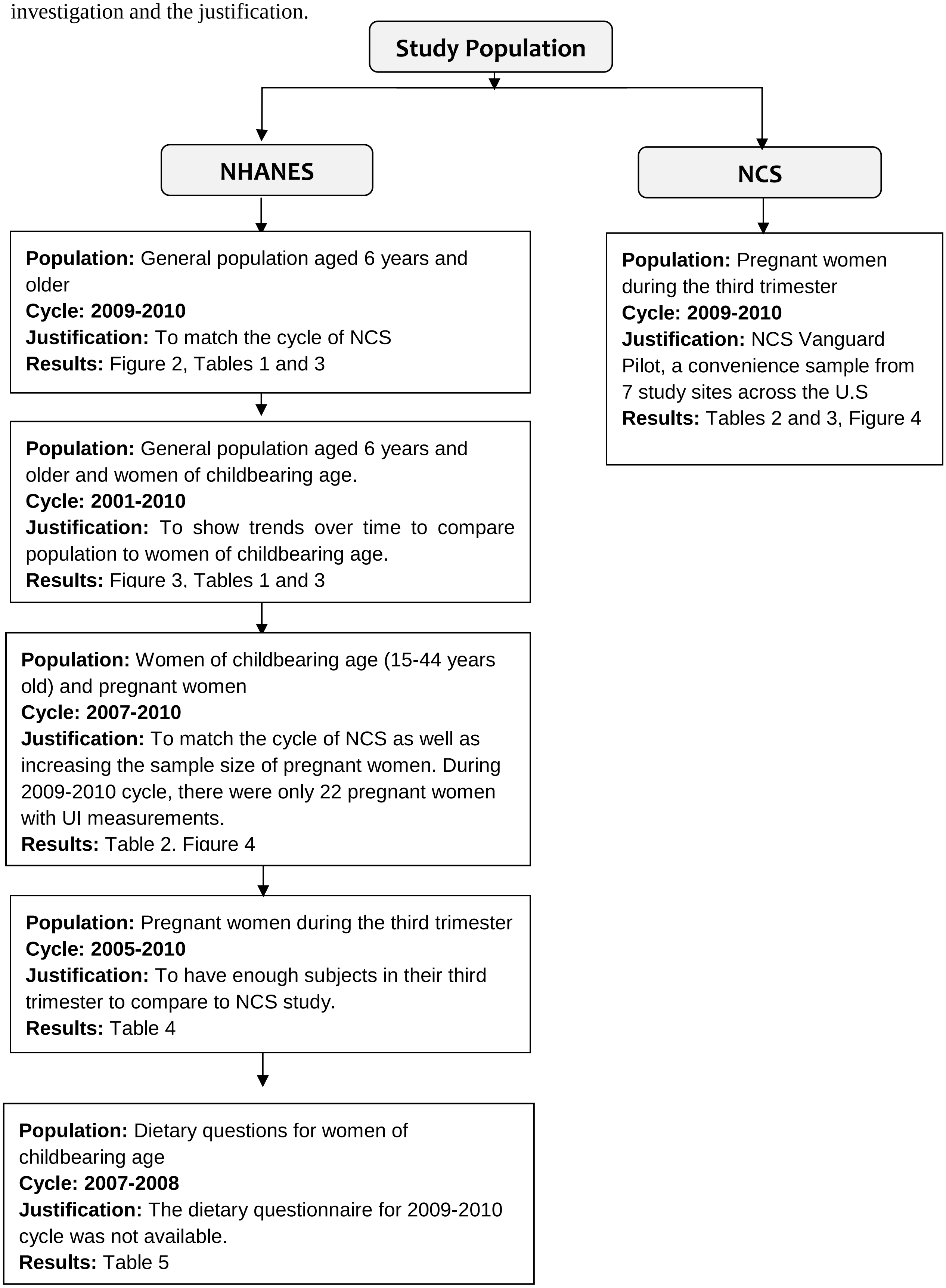
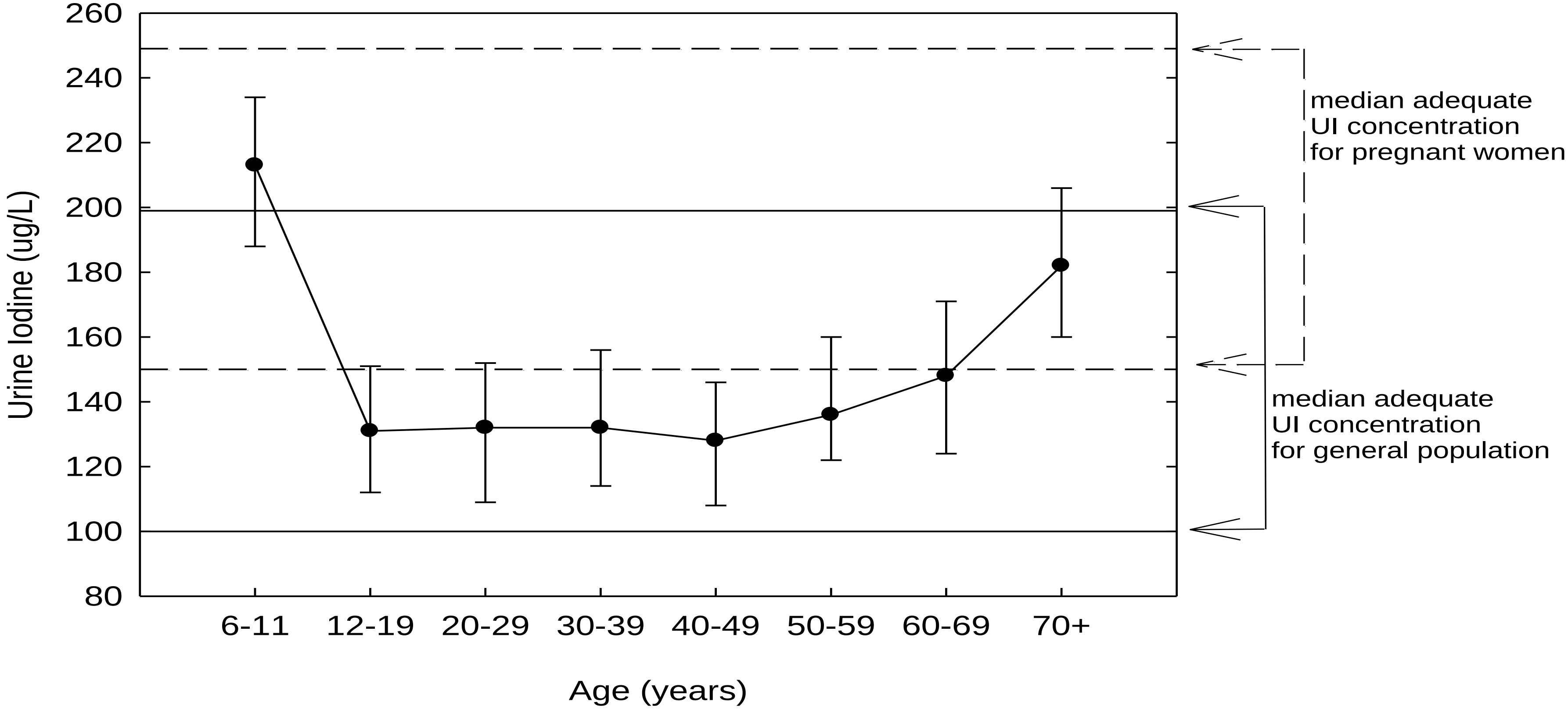
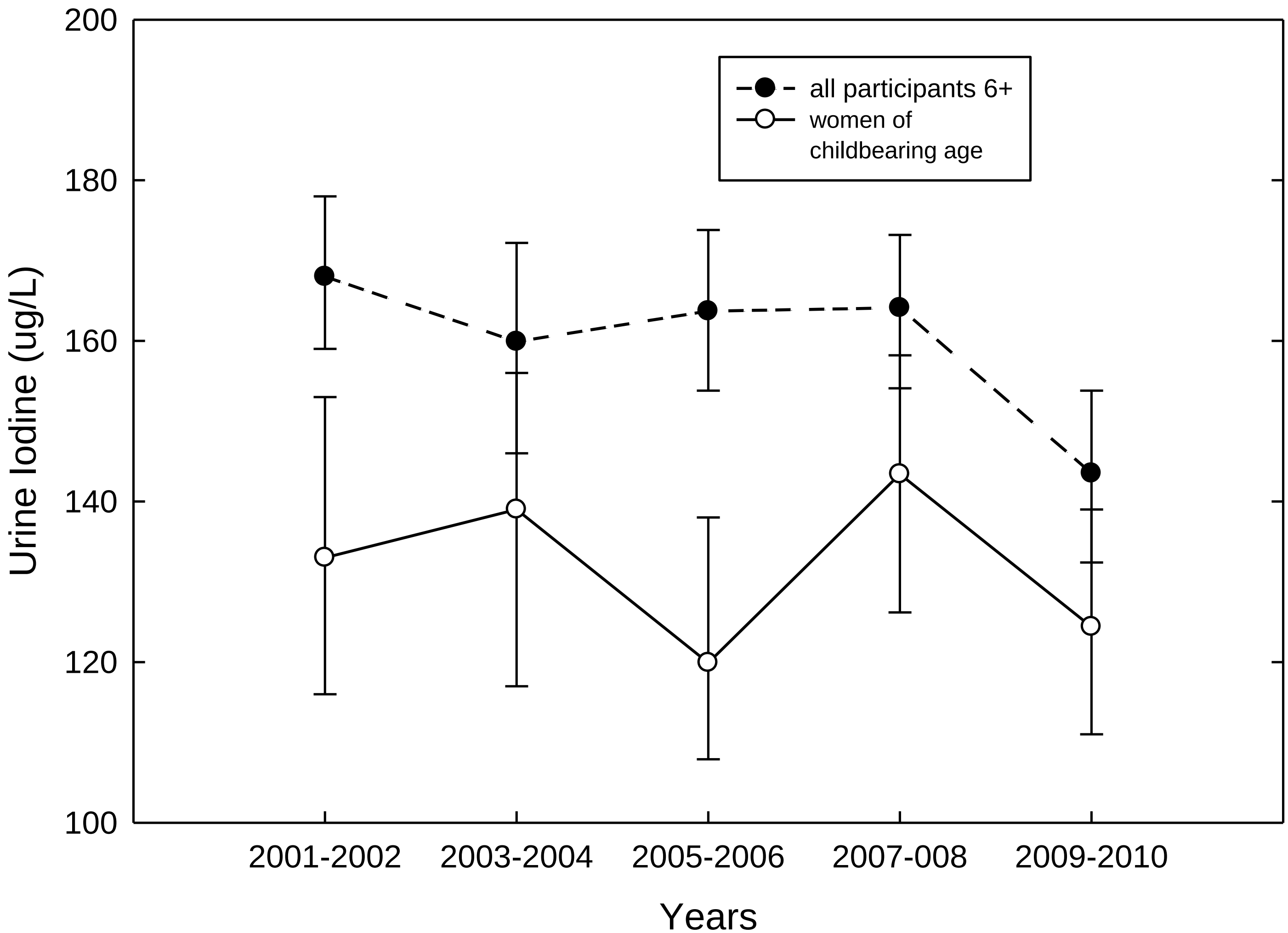


Figure 2. Median Urine Iodine (µg/L) by Age Category, NHANES 2009-2010 Participants 6 years and older



The solid horizontal reference lines indicate the adequate iodine intake range defined by WHO (100-199 µg/L) for the general population. The dashed horizontal reference lines indicate sufficient median iodine intake for pregnant women (150-249 µg/L)

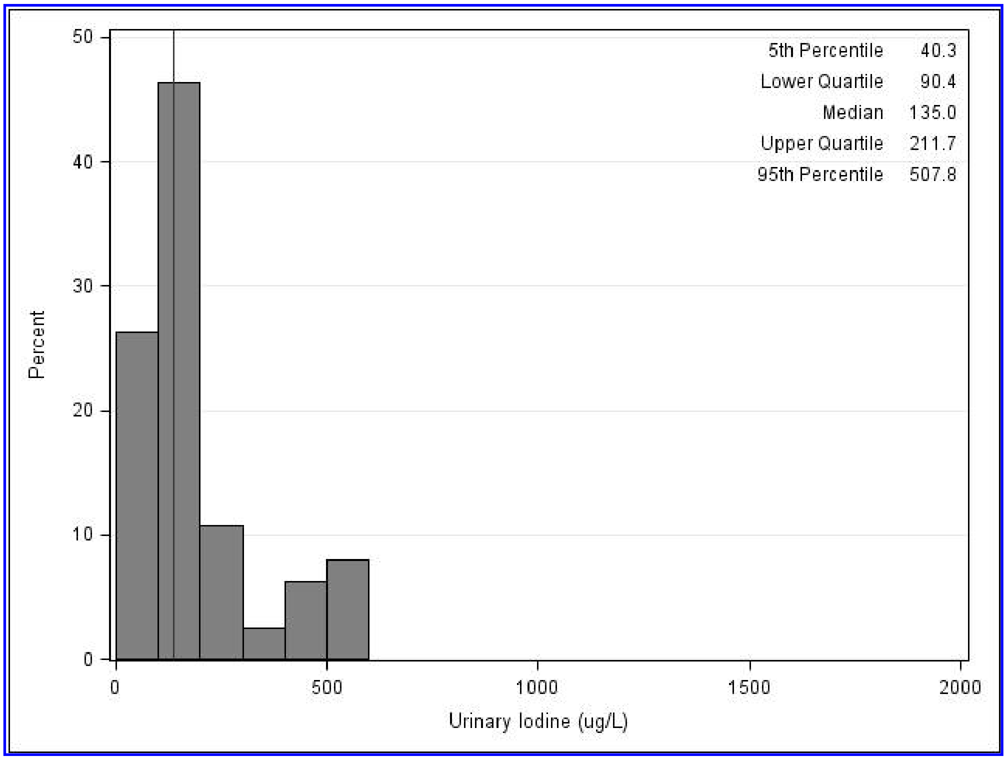
Figure 3 Median Urine Iodine (µg/L) for Participants older than 6 years and Women of Childbearing Age based on NHANES 2001-2010



Fgure 4A. Histogram of Urinary Iodine (µg/L) for Pregnant Women in NHANES 2007-2010 (N=76) (reference line denotes the median UI=135.0 µg/L)

Figure 4B. Histogram of Urinary Iodine (µg/L) for Pregnant Women (N=501) in the National Children's Study (reference line denotes the median UI=166.9 µg/L)

A)



B)

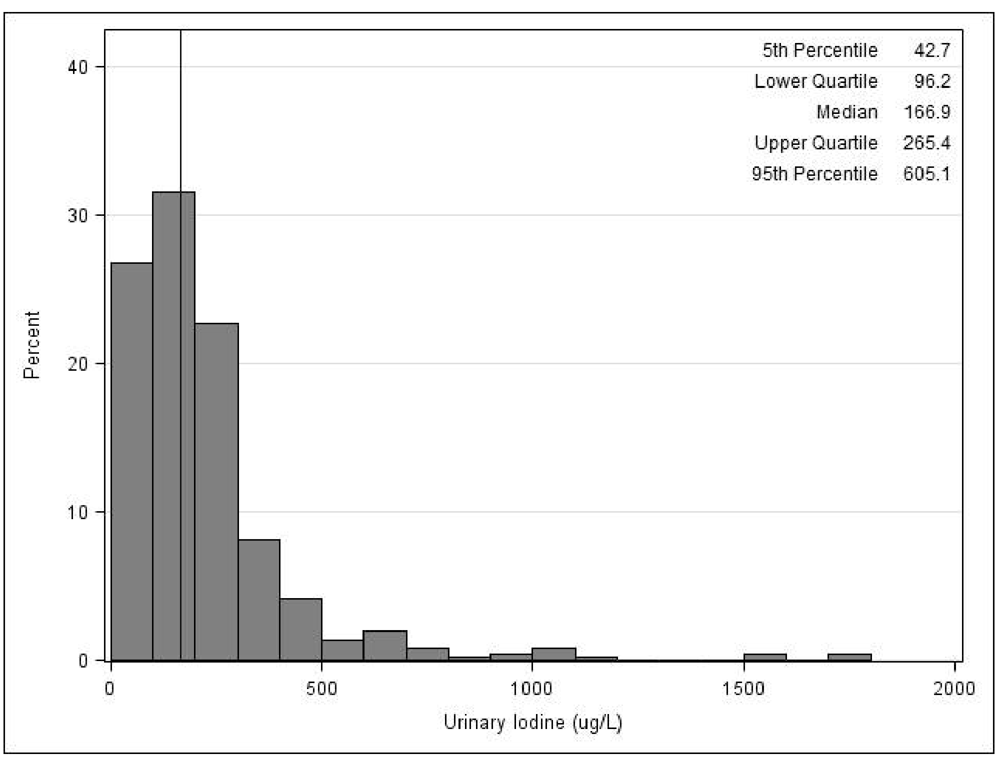
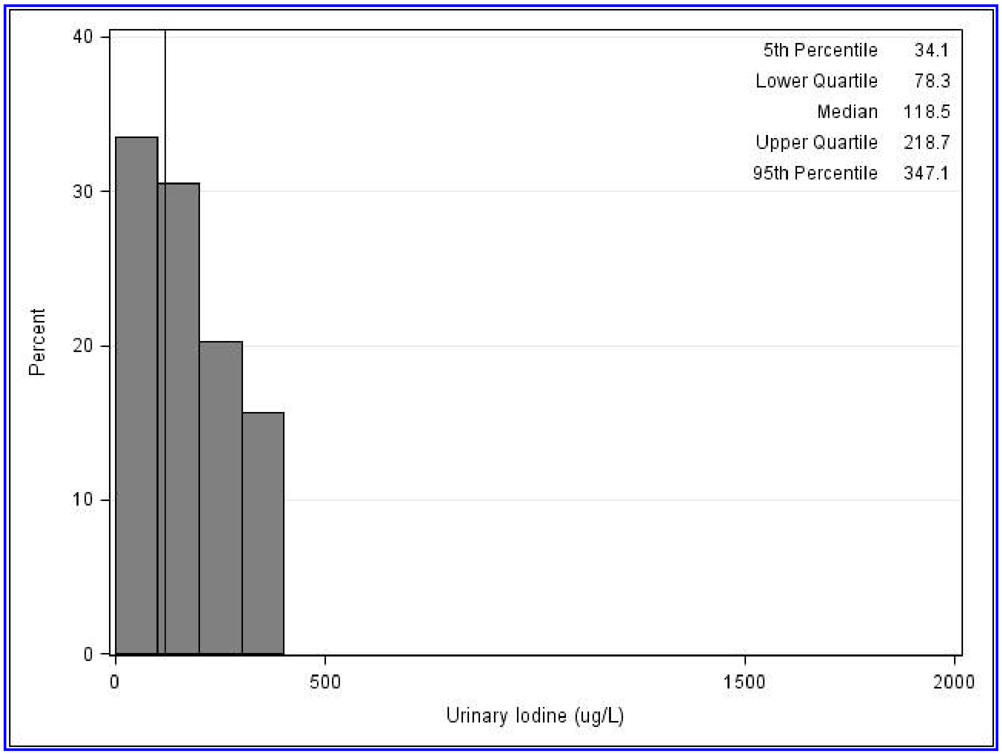


Figure 4C. Histogram of Urinary Iodine (μg/L) for Pregnant Non-Hispanic black Women, NHANES 2007-2010 (N=14) (reference line denotes the median UI=118.5 μg/L)

Figure 4D. Histogram of Urinary Iodine (μg/L) for Pregnant Non-Hispanic black Women (N=22) in National Children's Study (reference line denotes the median UI=133 μg/L)

C)



D)

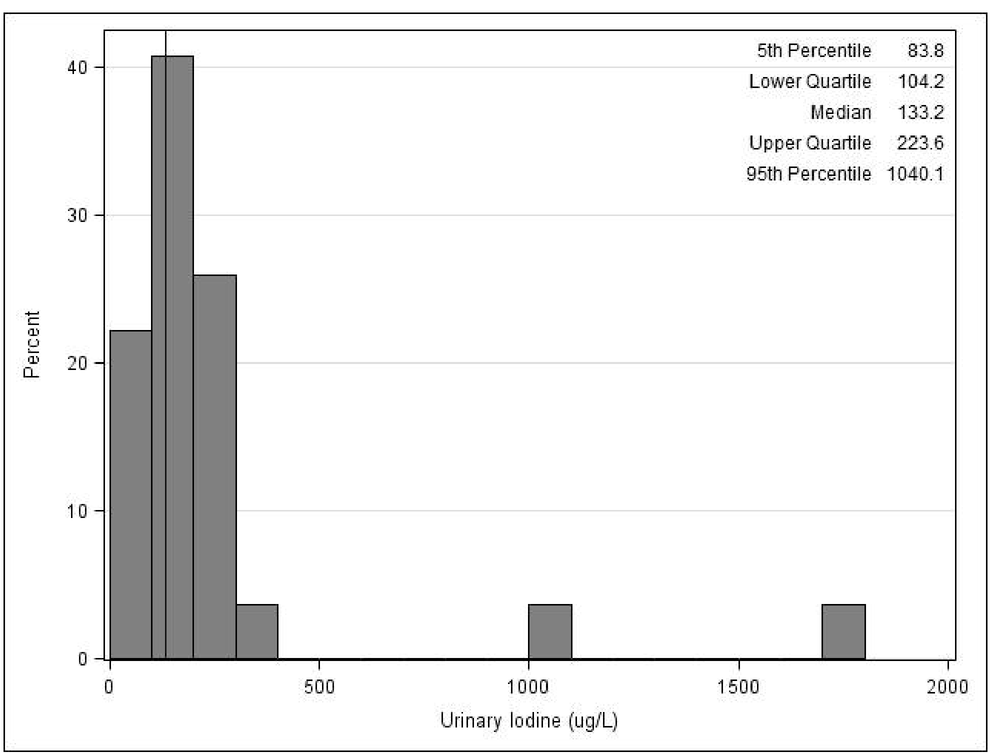


Table 1 Urinary Iodine and Iodine Corrected for Creatinine Levels by Age, Sex and Race/Ethnicity. Weighted Survey Analysis, NHANES 2009-2010

			UI (µg/L)	I/Cr (µg/g creatinine)
	N	**Weighted N**	**Median (95% CI)**	**Median (95% CI)**
Age				
6 years and above	2864	271,924,206	144(132-154)	143(136-148)
6-11 years	379	23,034,180	213(188-234)	250(221-279)
12-19 years	454	32,605,343	131(112-151)	117(107-130)
20-29 years	328	41,055,524	132(109-152)	112(98-129)
30-39 years	361	39,145,156	132(114-156)	114(102-129)
40-49 years	368	42,930,574	128(108-146)	114(101-137)
50-59 years	300	40,067,968	136(122-160)	147(128-170)
60-69 years	316	27,097,884	148(124-171)	181(154-210)
70 years and above	358	25,987,578	182(160-206)	239 (195-264)
Sex				
Male	1402	132,645,050	152(139-171)	135(126-142)
Female	1462	139,279,157	134(125-146)	150(143-162)
Race/Ethnicity				
Non-Hispanic white	1224	176,420,426	147(133-160)	149(143-159)
Non-Hispanic black	545	32,383,034	131(120-144)	98(89-105)
All Hispanic	914	41,172,201	148(134-160)	142(137-149)
Women of Childbearing Age	605	61,583,168	124(111-139)	117(108-127)

Table 2 Median and low UI concentrations in the U.S Women of Childbearing Age (15-44 years) by Pregnancy Status, NHANES 2007-2010 compared to NCS

			<150(μg/L)			<100(μg/L)			<50(μg/L)		
	N	**Median (95% CI)**	**%**	**SE**	**N**	**%**	**SE**	**N**	**%**	**SE**	**N**
NHANES Total	1568	133 (121-143)	56.3	2.2	862	36.9	1.9	550	15.4	1.8	205
NHANES Pregnant	76	135 (109-172)	55.8	7.7	45	26.3	6.5	26	15.7	6.6*	13
NHANES Nonpregnant	1492	133 (121 -143)	56.3	2.2	817	37.3	1.9	524	15.4	1.9	192
NCS Pregnant	501	167 (151-185)	45.3	2.3	227	26.7	1.9	134	7.0	1.5	35

* The relative standard error > 30%. The NHANES guideline

SE: Standard error, CI: confidence interval, UI: urinary iodine

Table 3 Median UI Concentrations (µg/L) for Women of Childbearing Age and Pregnant Women by Trimester, NHANES 2005-2010

Category	N	UI Median (95% CI)
Total	2233	129(120-136)
Pregnant	206	129(101-173)
Non-Pregnant	2027	129(119-136)
Trimester 1	42	109(50-219)
Trimester 2	70	128(88-219)
Trimester 3	64	172(109-267)

Table 4 Comparison of Urinary Iodine Levels by Race/Ethnicity and Age groups in The United States

Age Groups	NHANES 2009-2010				NCS		
6-11 Years	Race/Ethnicity	N	UI Median (µg/L) (95% CI)	I/Cr (µg/g creatinine) (95% CI)	N	UI Median (µg/L) (95% CI)	I/Cr (µg/g creatinine) (95% CI)
	Non-Hispanic white	109	241 (193-281)	285 (227-360)			
	Non-Hispanic black	84	168 (120-223)	163 (120-226)			
	All Hispanic	159	198 (153-254)	238 (216-268)			
12-19 Years	Race/Ethnicity						
	Non-Hispanic white	164	141 (107-162)	125 (113-139)	**		
	Non-Hispanic black	97	130 (107-155)	86 (72-109)	**		
	All Hispanic	162	150 (124-165)	132 (113-145)	**		
20+ Years	Race/Ethnicity						
	Non-Hispanic white	951	143 (128-158)	147 (137-159)	327	179 (157-199)	208 (196-227)
	Non-Hispanic black	364	129 (117-144)	94 (84-101)	22	132 (104-221)	97 (86-189)
	All Hispanic	593	137(125-156)	137 (126-144)	86	178 (136-209)	152 (135-177)
12+ Years	Region						
	North Carolina				82	217 (177-251)	169.4 (141.4-210.1)
	South Dakota/Minnesota				102	205 (161-225)	203.1 (177.9-242.7)
	Pennsylvania				45	125 (107-199)	196.4 (161.2-311.7)
	California				62	107 (86-147)	144.7 (121.4-195.2)
	New York				39	150 (86-186)	149.7 (126.3-189.6)
	Utah				102	190 (168-209)	197.5 (162.7-219.5)
	Wisconsin				69	145 (112-193)	241.2 (205.5-286.9)

*NHANES = National Health and Nutrition Examination Survey; NCS=National Children's Study

** NCS 12-19 Years has frequencies that fall below the disclosure threshold.

Table 5. Urinary Iodine **Median and 95% CI (UI) (μg/L) by Race and Dairy Product, Salt, Fish and Fish/Shellfish Consumption in Women of Childbearing Age NHANES 2007-2008**

Race	Dairy Consumption	N	Weighted Percent (%)	Median UI (95% CI)	P-value
Non-Hispanic white	Never or Rare	149	27.1	111 (90-142)	0.0001
	Not Often	167	31.1	131 (99-165)	
	Often	216	41.8	189 (163-204)	
Non-Hispanic black	Never or Rare	126	39.8	111 (82-132)	0.0009
	Not Often	89	27.9	109 (89-163)	
	Often	101	32.3	151 (110-212)	
All Hispanic	Never or Rare	153	31.1	134 (106-155)	<0.0001
	Not Often	133	27.2	163 (130-196)	
	Often	210	41.7	185 (155-207)	
	Salt consumption				
Non-Hispanic White	Never or Rare	142	27.1	110 (91-149)	0.07
	Not Often	188	37.1	144 (116-189)	
	Often	183	35.9	148 (113-185)	
Non-Hispanic Black	Never or Rare	77	24.5	117 (93-161)	0.2
	Not Often	97	29.5	132 (82-195)	
	Often	136	45.9	116 (97-132)	
All Hispanic	Never or Rare	78	17.2	154 (124-239)	0.2
	Not Often	128	27.1	152 (124-182)	
	Often	255	55.6	165 (141-194)	
	Fish/Shellfish consumption				
Non-Hispanic White	Yes	353	70.6	144(114-178)	0.6
	No	159	29.4	134(100-175)	
Non-Hispanic Black	Yes	244	81.7	119(99-151)	0.5
	No	66	18.3	123(83-159)	
All Hispanic	Yes	339	73.4	166(153-185)	0.03
	No	128	26.6	146(108-185)	

*p-value tests whether the median UIs were significantly different among "Never or Rare", "Not Often" and "Often" dairy, and salt consumption groups within each race/ethnicity group. P-value tests whether the median UIs were significantly different among ""yes" or "no" for fish/shellfish consumption during the past 30 days within each race/ethnicity group.