Association between Urinary Iodine Concentrations And Insulin Resistance in US Adults

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The undersigned, appointed by the Dean of the Graduate School, have examined the thesis entitled

ASSOCIATION BETWEEN URINARY IODINE CONCENTRATIONS AND INSULIN RESISTANCE IN US ADULTS

Presented by Chisom Ezemaduka

A candidate for the degree of Master of Science

And hereby certify that, in their opinion, it is worthy of acceptance.

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DEDICATION

To God Almighty,

Who is my glory, my shield and the lifter of my Head (Psalm 3:3),

My family,

And all who practice and promote good nutrition.

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To God be all the honor, glory and praise as the author and source of all wisdom and ideas. He has been my strength and only by His grace have I prevailed.

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LIST OF ABBREVIATIONS

BMI – Body mass Index

CVD – Cardiovascular Disease

ID – Iodine Deficiency

IDDs – Iodine Deficiency Disorders

IR – Insulin resistance

FBG – Fasting Blood Glucose

HbA1C – Glycated Hemoglobin A1C

HOMA-IR – Homeostatic Model Assessment IR

MetS – Metabolic Syndrome

mUIC – Median Urinary Iodine Concentration

NHANES – National Health and Nutrition Examination Survey

SCH – Subclinical hypothyroidism

T2D – Type 2 Diabetes

T3 – Triiodothyronine

T4 – Thyroxine

TG – Thyroglobulin

TH – Thyroid hormone

TSH – Thyroid Stimulating Hormone

UIC – Urinary Iodine Concentration

WHO – World Health Organization

ABSTRACT

Background: Iodine intake within the US population has declined in recent years. Mild iodine deficiency increases the risk of inadequate thyroid hormone production and there is growing evidence that sub-clinical hypothyroidism may give rise to outcomes disruptive to metabolic health including insulin resistance (IR).

Objective: To investigate the association between urinary iodine concentrations (UIC), a measurement of iodine status, and IR in US adults.

Method: Data from 1286 US adults (≥ 20years) in the NHANES 2011-2012 were used in the study. Two subgroups (low= UIC < 100µg/L and normal=UIC ≥ 100µg/L) were compared for measures of IR, including fasting blood glucose (FBG), hyperinsulinemia, and glycated hemoglobin. Chi-square test, simple linear regressions and multiple logistic regressions were used to test for statistical differences between the groups.

Results: Median UIC (mUIC) of adults was optimal although women, high income earners, age groups 40-59yrs and non-iodine supplements users had significantly lower mUIC ($P < 0.05$). In males, no significant associations were noted between measures of IR and UIC. Females with low UIC were at greater risk for FBG ≥5.6mmol/L (adjusted odd ratio (AOR) = 1.73, 95% confidence interval (CI) = 1.09 – 2.72) while those with normal UIC were at greater risk for HbA1C ≥5.7% (OR= 0.56, 95% CI = 0.34 – 0.90) and HOMA-IR ≥ 2.6 (AOR= 0.56, 95% CI = 0.32 – 0.99).

Conclusion: Our results partially support our hypothesis that UIC is associated with the odds of IR. Adult females with low UIC had a greater risk for elevated FBG, a marker of prediabetes, while those with normal UIC had greater risks for elevated HbA1C and HOMA-IR. Further investigations are warranted to elucidate the casual relationship between iodine status and IR.

CHAPTER 1

INTRODUCTION

1.1 Statement of Problem

1.1.1 Decreased Intake of Iodine Food Sources

Iodine is an essential element necessary for thyroid hormone (TH) production (Vanderpras and Moreno-Reyes, 2017. The Food and Nutrition Board (FNB) of the Institute of Medicine (IOM), recommends dietary iodine intake of 150ug/day for nonpregnant, nonlactating adults (Zimmermann et al., 2009).

Iodine intake within the U.S. population has declined from 250ug/day to 157ug/day (Salt Institute, 2013) and iodized salt sales declining from 70% to 53% (Maalouf et al., 2015) in recent years. The speculative reasons for this decline are replacement of home-prepared foods with commercially prepared foods made with non-iodized salts (Ershow, 2018) and increased preferences for other salt types for cooking which are non-iodized (William, 2009). All these have raised concerns about potentially inadequate intakes of iodine despite high intakes of salt from foods (NIH, 2010). Although several measures are available, urinary iodine concentration (UIC) is a well-accepted, cost-efficient and easily obtainable indicator of iodine status (Cavalieri, 1997).

1.2.2 Iodine deficiency: Beyond Goiter and Cretinism

Classical iodine deficiency is a well-documented health problem. The World Health Organization (WHO) rates it among the top three micronutrient deficiencies worldwide (Delange, 2000). For the community, they impose wasted reproductive effort, impaired economic productivity and increased health costs (Dunn, 2009). A consequence of deficient

iodine intake is hypothyroidism (Duntas and Brenta, 2012; Starr, 1962); and if not corrected, is associated with goiter, reproductive damage, fetal and infant mortality, and neurologic defects, Although there are currently limited cases of iodine deficiency in form of goiter in the U.S population, there is growing evidence that sub-clinical hypothyroidism (SCH) may give rise to outcomes disruptive to metabolic health as any little iodine deficiency increases the risk of inadequate thyroid hormone production (Wang et al., 2018). This has been associated with cardiovascular disease risk factors (Zimmermann *et al.*, 2009) as well as development of breast cancer (Ahad and Ganie, 2010). More recently, however, evidence has been presented for a connection between SCH and conditions related to metabolic syndrome (MetS)

1.2.3 Impact of SCH on Metabolic Syndrome and Related Conditions

The prevalence of MetS has grown over time, paralleling the rise in obesity rates, and is now reaching epidemic proportions. In Western countries, the estimated prevalence of MetS is approximately one-fifth of the adult population, and this increases with increasing age (Beltran-Sanchez et al., 2013). MetS is characterized by abdominal obesity, hypertension, elevated blood lipids and insulin resistance (IR) (Meigs, 2003).

Iodine, through the action of TH, modulates numerous metabolic processes (Reinehr, 2010). Elevated plasma levels of total cholesterol and low-density lipoprotein (LDL) have been demonstrated in subjects with serum TSH >10mU/L (Duntas and Wartofsky, 2007) increasing the risk of coronary heart disease or premature death if not monitored and corrected (Rodondi 2006, Asvold, 2007, Asvold, 2008). Several studies have reported an association between higher free triiodothyronine (fT3) to increased waist circumference and lower insulin sensitivity (De Pergola et al., 2007; Roef et al., 2012). Furthermore, a cross-sectional study reported significant

association of low total triiodothyronine (TT3) and low free T3 (FT3) with increased IR (Wang et al., 2018).

Considering that the prevalence of both iodine deficiency and MetS remain high among subgroups in the US (Caldwell et al., 2013; Amouzegar et al., 2015; Garduno-Garcia et al., 2015), further exploration of the association between these two states is warranted. A few studies have used NHANES data to show associations between both TH status and iodine status in the context of dyslipidemia (Lee et al., 2016; Ram, 2017; Le et al., 2016) and there is one published investigation examining the link between TH and IR (Wang et al., 2018). *However, there is no study to the best of my knowledge that has assessed the association directly between iodine status as measured by urinary iodine concentration (UIC) and IR using NHANES.* This study, therefore, will assess the association between UIC and IR in US adults using NHANES (2011-2012).

1.2 Specific Aim

To investigate the association between urinary iodine concentrations and insulin resistance in US adults using NHANES (2011-2012 cycle).

1.3 Hypothesis: UIC is associated with the odds of IR in the US population

1.4 Objectives

Using NHANES data collected 2011-12 cycle, the objectives of this study are to:

- Identify socioeconomic and lifestyle variables affecting UIC and markers of IR (fasting glucose, insulin, HOMA-IR, HbA1C)
- Determine the association of UIC with markers of IR

- Estimate the risks for IR by UIC

1.5 Significance

The study described herein seeks to establish a baseline for future studies on the association of iodine and metabolic health. In addition, it will serve as an evidence-based tool for Registered Dietitian Nutritionists (RDNs), other health care providers, and scientists in communicating the impact of the iodine intake in human health.

CHAPTER 2

EXTENDED REVIEW OF LITERATURE

2.1 Insulin Resistance in MetS: Prevalence and Link to Iodine.

Insulin resistance (IR) is defined as an inability of insulin to increase glucose uptake and utilization in peripheral tissues (muscles, adipose tissue, and liver) inducing beta-cell dysfunction (Robertson, 1995; Taylor, 2012). IR is considered as an important health issue with major roles in the development of metabolic syndrome (MetS) (Shoshtari-Yeganeh, 2019).

The National Cholesterol Education Program Adult Treatment Panel III (2001) defines MetS as ≥3 of the following risk factors occurring together: abdominal obesity measured by waist circumference; atherogenic dyslipidemia; hypertension; and IR. The prevalence of MetS has increased over time and is now reaching epidemic proportions. In Western countries, the estimated prevalence of MetS is approximately one-fifth of the adult population, and this increases with age (Beltran-Sanchez et al., 2013). Moreover, the importance of MetS lays in its associated risk of cardiovascular disease (CVD) and type 2 diabetes (T2D) as well as other harmful conditions such as nonalcoholic fatty liver disease (Perez-Martinez et al., 2017).

The popular clinical cutoff for HOMA-IR is ≥ 2.60 (Qu et al., 2011). Fasting blood glucose (FBG) and fasting insulin are predictors of IR levels and subsequently used in homeostatic model assessment (HOMA-IR) calculations ((Matthews et al., 1985), a common method used to quantify IR (Smerieri et al., 2015). A FBG ≥ 5.6mmol/L (Taylor, 2012) and fasting elevated insulin > 9.0 μU/L (Johnson et al., 2010) have been reported to predict IR. By prevalence, IR increases with age from about 7% in persons of 20years old to over 40% in persons older than 60years (Meigs, 2003). By ethnicity, Non-Hispanic Black (NHB) and

Hispanics have higher IR prevalence rates by 11.8% and 12.6% respectively compared to Non-Hispanic Whites (NHWs) and Asian Americans with prevalence rates of 7.1% and 8.4% respectively (Spanakis and Golden, 2013). According Gaskin et al., 2014, prediabetes and diabetes are higher in low income communities compared to communities with high income ratio. In a report by McLaughlin et al., 2004, 36% of individuals in the most IR tertile were obese with body mass index (BMI) $\geq 30 kg/m^2$.

Along with several risk factors (including physical inactivity and genetics), poor nutrition status is associated with increased risk for developing IR (Meigs, 2003). One such nutrient inadequacy that may be involved is iodine as it is known to play a role in insulin sensitivity via T3 (Weinstein et al., 1994; Potenza et al., 2009; Brent, 2012); and low iodine status has been associated with increased IR (Wang et al., 2018; Bougle et al., 2014). Thus, the monitoring and further exploration of iodine status as it relates to IR appears to be needed.

2.2 Iodine (History & Discovery)

In 1895, Baumann characterized iodine as an essential element of the thyroid tissue (Vanderpras and Moreno-Reyes, 2017). Iodine was discovered by Barnard Courtois (A French Chemist) in 1811 upon extraction of sodium (Na) and potassium (K) compounds from seaweed ash (Education.jlab.org). He accidentally added too much acid and a violet colored cloud erupted from the ash. The gas condensed on metal objects in the room, creating solid iodine. Iodine was given its name from the Greek word for *violet*.

Iodine is an element with atomic number 53 and atomic weight of 126.9 (Dunn, 2003). It is the densest among the common halogens. It consists of solid-blue black crystals with a melting

point of 113.6^{o}C and oxidation states of -1, +1, +3, +5, +7. It is sparingly soluble in water and has high soluble in many organic solvents.

Iodine is used to test for starch which turns deep blue when there is contact between them. Potassium iodide (KI) is used to make photographic film. Iodine mixed in alcohol acts as an antiseptic for external wound treatment. Iodine-131 (radioactive isotope) is used to treat some thyroid gland diseases. Pure iodine is poisonous if ingested.

The human body requires trace amounts of iodine for survival. Iodine when ingested into the human body is used in the production of thyroid hormones (T4 also called Thyroxine and T3 known as 3, 5, 3'-triiodothyronine) through a process cycle (Rohner et al., 2014). T3 is the active form of the thyroid hormones (Hays, 1984).

2.3 Food sources of Iodine and Recent Declines in Iodine Intakes in US

Generally, Iodine is naturally low in most foods and beverages. Common food sources provide 3-80ug/serving (Rohner et al., 2014; Haldimann et al., 2005; Pennington et al., 1995) with content largely dependent on food's origin (Rohner et al., 2014). Saltwater fish and seafood are relatively high in iodine because of the ability of these animals and plants to concentrate iodine from seawater. However, due to irregular consumption of these seafoods as a result of cost, they do not contribute substantially to dietary iodine intake (Johner et al., 2011; Julshamn et al., 2001; Dahl et al., 2004). Seaweed is relatively high in iodine (Zimmermann, 2009) thereby providing high iodine concentrations to populations who consume as part of their diet (Zimmermann and Andersson, 2012; Teas et al., 2004; Nagataki, 2008).

Currently, iodized salt tends to be the major source of iodine in many countries around the world (Johner et al., 2011; Zimmermann, 2009; Zimmermann and Andersson, 2012; Charlton and Skeaff, 2011). According to nutrition label declarations, the iodine content in iodized salt ranges from 15-80mg/kg salt (Charlton and Skeaff, 2011; World Health Organization (WHO, 1996); Andersson et al., 2007) though reports have shown a correlation between iodine loss and humidity. A study on several salt brands reported rapid loss of iodine from the products within four (4) weeks after exposure to air upon opening (Dasgupta et al., 2008). The researchers from this study further reported that this loss is faster with higher humidity which can decrease the recommended intake for an individual.

Iodophors used as disinfecting agent and teat dips during dairying contribute to iodine found in dairy foods especially liquid milk although it varies depending on the amount of iodophors used (Haldimann et al., 2005; Pearce et al., 2004; Dahl et al., 2003; Li et al., 2006; Schone et al., 2009). Iodine content of supplemented animal feeds also reflects the iodine content of dairy foods (Castro et al., 2012; Flachowsky et al., 2014). However, individuals whose diet excludes or restricts iodine rich food sources (such as vegans/ vegetarians or lactose intolerance) may be at risk for iodine deficiency (Booms, 2016). Additionally, seaweed food additives like agar-agar, carrageenan, alginates also contain trace amounts of iodine (Chung et al., 2013).

Some Supplements contain iodine in the form of potassium iodate, but small sub-sample of the population has been shown to take them. A data from NHANES (2001-2006) reported that only one fifth of 4322 non-pregnant women surveyed were taking supplements that contained iodine (Gregory et al., 2009).

2.4 Recommended Dietary Requirements and Tolerable Upper Intake Level

The Food and Nutrition Board (FNB) of the Institute of Medicine (IOM) recommends 150ug/day iodine dietary allowance for nonpregnant non-lactating adults (Zimmermann et al., 2009). However, iodine requirements by age and life stage are shown in (**Table 2.1**). The Adequate Intake (AI) for infants are based on observed mean intakes by healthy full-term breast-fed infants in iodine sufficient areas (Rohner et al., 2014). The Tolerable upper intake level (UL) for iodine which is used as a reference for safety for no risk of adverse health effects (Zimmermann and Kohrle, 2002) is shown in (**Table 2.2**). Some factors responsible in the derivation of recommended intake for iodine point to amount of iodine needed to prevent goiter, provide the lowest serum TSH as well as calculations from the amount of replacement T4 necessary to achieve euthyroidism in athyreotic subjects and disposal rates of administered T4 (Delange, 1993; Dunn, 2000; Rohner et al., 2014)

TABLE 2.1 Recommendations for Iodine Intake by Age and Life Stage

	Institute of Medicine	
Life-stage group	**EAR**	**AI or RDA**
	(µg/d)	(µg/d)
Infants 0-12months	------	110-130
Children 1-8years	65	90
Children 9-13years	73	120
Adults ≥ 14years	95	150
Pregnancy	160	220
Lactation	200	290

Data from references Institute of Medicine (IOM), 2001. AI, Adequate Intake; EAR, Estimated Average Requirement; RDA, Recommended Dietary Allowance.

TABLE 2.2 Tolerable Upper Intake Level for Iodine (UL)

Life-stage group	UL (µg/d)
1-3years	200
4-6years	300
7-10years	600
11-14years	900
Adult	1100
Pregnant and lactating women	1100

Data from references Institute of Medicine (IOM), 2001.

2.5 Intestinal Absorption and Cellular Uptake of Iodine

Dietary iodine in its organic form is converted mostly to iodide before efficient absorption in the gastrointestinal tract (Cavalieri, 1997; Hays, 1984). Under conditions of iodine adequacy, adults accumulate about 60ug iodine/day in the thyroid gland to account for losses and thyroid hormones (Thyroxine (T4) and 3, 5, 3'-triiodothyronine (T3)) production (Rohner et al., 2014). Upon consumption of iodine from the diet and liberation from the food matrix, it enters circulation for uptake by the thyroid or excretion by the kidney where more than 90% of iodide are excreted with only a small amount appearing in the feces (Zimmermann et al., 2008).

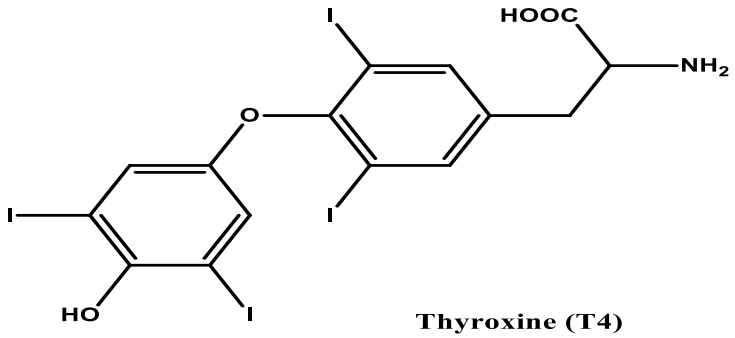
2.6 Process Cycle for Production of Thyroid Hormones via Iodine

Iodine is transported actively from the blood to the thyroid cell using a sodium/ iodide transporter (NIS) located at the thyroid basal membrane (Eskandari et al., 1997). Iodide then migrates to the apical membrane where it is oxidized to iodinate tyrosyl residues within the

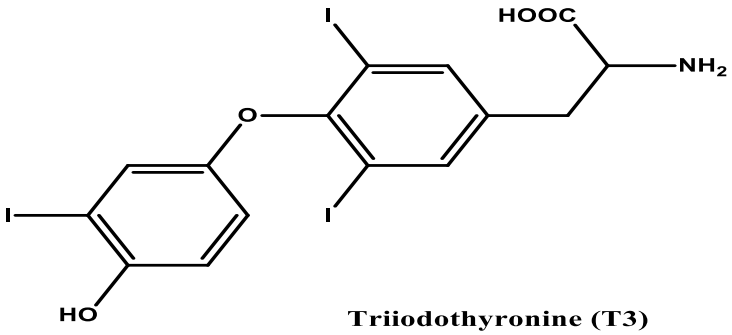
peptide chain of thyroglobulin. This occurs via a complex series of reactions requiring thyroperoxidase (TPO), hydrogen peroxide, reduced nicotinamide adenine dinucleotide phosphate (NADPH) and an NADPH oxidase (Dunn, 2000). Initial iodination which occurs within the peptide structure of the thyroglobulin produces iodotyrosine (MIT) and diiodotyrosine (DIT) (Cavalieri,1997). Further action of TPO forms T4 by coupling of two molecules of DIT and T3 by coupling a molecule each of MIT and DIT with T3 (**figure 2.1**) being the active form of the hormone (Rohner et al., 2014). The thyroid hormones are stored in the follicular lumen of the thyroid gland until needed or converted to reverse T3 (rT3) (Hays, 1984). Iodine makes up 65% and 59% of T4 and T3 respectively (Zimmermann, 2012). When needed, thyroid hormones attach to binding proteins and gets delivered to target tissues for regulation of energy metabolism (Berry et al., 1989; Harper et al., 1993; al-Adsani et al., 1997; Boivin et al., 2000), thermogenesis (Seydoux et al., 1982; Bianco and Silva 1987; Mory et al., 1981; Carvalho et al., 1991; Silva 2003), cholesterol metabolism (Duntas, 2005; Espenshade and Hughes 2007; Duntas and Brenta, 2012;), normal development and growth (Vejbjerg et al., 2007) as well as glucose metabolism (Potenza et al., 2009; Brent, 2012). Iodotyrosine dehalogenase regenerates iodide from unused MIT and DIT for reuse within the thyroid or release into the blood accounting for the iodide leak in state of chronic Iodine excess and certain thyroid disorders (Cavalieri, 1997).

Thyroid secreting hormone (TSH) otherwise called thyrotropin produced in the pituitary controls the production, secretion of the thyroid hormones and conversion of T4 to T3 (Dumont and Vassart, 1995; Rapoport and Spaulding, 1996). TSH effects are mediated by the G protein-adenylate cyclase-protein kinase A cascade (PKA) (Cavalieri, 1997). TSH opens the apical iodide channel to increase iodide efflux from cell to colloid as well as increase the synthesis of thyroglobulin, TPO via the cyclic AMP (cAMP) cascade action at the level of transcription

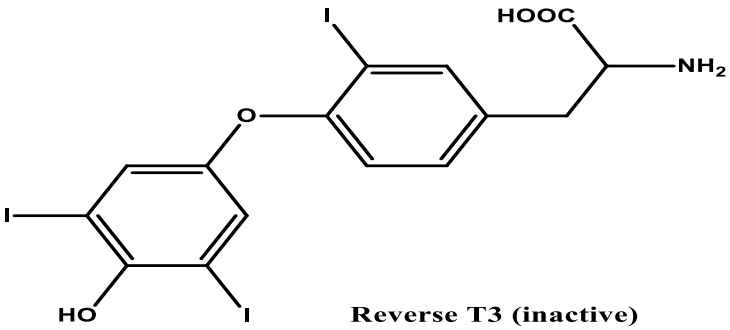
(Cavalieri, 1997). TSH is controlled by thyrotropin-releasing hormone (TRH) which is secreted by the hypothalamus and responsive to TH and TSH feedback.



Thyroxine (T4)



Triiodothyronine (T3)



Reverse T3 (inactive)

FIGURE 2.1 Structures of thyroid hormones

2.7 Deiodinases: Regulation of Thyroid Hormone Activation

Deiodinases are enzymes of cellular thyroid activity that determine intracellular activation and deactivation of thyroid hormones (Bianco et al., 2002). There are three different

deiodinases present in body tissues namely: Type 1 deiodinase (D1), Type II deiodinase (D2), and type III deiodinase (D3) (Koenig et al., 1984; Peeters et al., 2005). The activity of each type of deiodinase changes in response to differing physiologic conditions and this result to different tissue levels of T4 and T3 under different conditions (Kaplan, 1984; Peeters et al., 2005).

2.7.1 Deiodinase Type I (D1)

D1 converts inactive T4 to active T3 throughout the body with high levels in the liver, kidney and thyroid (Mullur et al., 2014). It has no significant control in the pituitary T4 to T3 conversion which is dominantly controlled by D2 (Bianco et al., 2002; Campos-Barros et al., 1996). D1 expressed in the cell membrane converts T4 by outer ring deiodination (ORD) to bioactive T3 (Schneider et al., 2006). In response to different physiologic conditions like physiologic and emotional stress, depression, dieting, weight gain, leptin resistance, insulin resistance, obesity and diabetes, chronic pain and exposure to toxins, D1 is suppressed and down-regulated (decreasing T4 to T3 conversion) in all tissues except the pituitary (Chopra et al., 1975; Linnoila et al., 1982; Fontana et al., 2006; Araujo et al., 2009; Islam et al., 2008; Morley, 1981; Lema et al., 2008). Furthermore, D1 activity has been observed lower in females making them more prone to hypothyroidism (Miyashita et al., 1995; Harris et al., 1979).

2.7.2 Deiodinase Type II (D2)

D2 is expressed in the endoplasmic reticulum of the brain, pituitary, thyroid and brown adipose tissue (BAT) which preserves T3 in these tissues as serum T4 levels fall (Mullur et al., 2014; Maia et al., 2005). D2 is primarily responsible for rapid increases in intracellular T3 in specific tissues which is transferred to the nucleus to regulate gene transcription (Maia et al., 2005). D2 activity is also critical for signaling and synergism of TH in the regulation of thermogenesis in BAT (Silva, 2005). In addition, D2 is critical in the T4-mediated negative

feedback loop regulated via the hypothalamic-pituitary Axis (HPA) (Arrojo e Drigo et al., 2011) where negative feedback response is promoted by an increase of D2 activity in the pituitary (Rosene et al., 2013). Furthermore, D2 is stimulated and upregulated in response to various physiologic conditions like emotional stress, depression, dieting, weight gain, diabetics and systemic illness by increasing intra-pituitary T4 to T3 conversion (German et al., 2011; Gereben et al., 2008; Goldman et al., 2009). The finding that stimulation of D2 activity by bile acids through activation of the G protein-coupled receptor for bile acids (TGR5) receptor links TH action with bile acid signaling (Watanabe et al., 2006). Administration of bile acids to mice resulted in increased energy expenditure in BAT, prevented obesity and improved insulin sensitivity. The TGR5 which is expressed in the human adipose tissue has a correlation with basal metabolic rate upon expression (Svensson et al., 2013).

2.7.3 Deiodinase Type III (D3)

D3 is expressed at high levels on the cell membrane of the skin, vascular tissue and placenta (Mullur et al., 2014). D3 activity converts T4 by inner ring deiodination (IRD) to inactive reverse T3 (rT3) (Peeters et al., 2005; Chopra et al., 1975). Reverse T3 acts as a competitive inhibitor of T3 by blocking T3 from binding to its receptor and blocking T3 effect (Okamoto et al., 1997; Benvenga et al., 1993) and blocks T4 and T3 uptake into the cell (Mitchell et al., 1999). D3 expression in the placenta protects a developing fetus from excessive maternal TH (Mullur et al., 2014).

2.8 Assessment of Iodine Status

According to Rohner et al., 2014 and Pironi et al., 2015, the most useful methods to assess iodine nutrition fall into three categories:

1) **Thyroid function tests (T4, T3, TSH, thyroglobulin Tg).** This approach measures intermediate iodine intake (weeks to months). TSH is considered to be a better indicator for newborn screening for congenital hypothyroidism (Delange, 1997; Rohner et al., 2014). Due to higher rates of iodine turnover in neonates, there is increased TSH stimulation in low iodine supply to maintain this turnover (Zimmermann, 2008). In most population, TSH values above the threshold of 5mU/L in whole blood collected 3-4 days after birth suggest iodine deficiency in the population (Zimmermann et al., 2003; WHO, 2007).

   In iodine-deficient population, serum T3 increases or remains unchanged while serum T4 usually decreases although these changes are often within the normal range (Zimmermann, 2008; Rohner et al., 2014). For Tg, small amounts are usually secreted into circulation iodine sufficiency with concentration <10µg/l. However, in severe iodine deficiency, serum Tg increases due to increased TSH stimulation and greater thyroid cell mass.

2) **Thyroid size.** This measures long-term iodine nutrition (months to years). Thyroid size assesses the presence of goiter using neck inspection and palpitation by measuring the volume of the thyroid's lateral lobe in compared to the terminal phalanx of the thumbs of the subject being examined (Zimmermann, 2008). According to the classification system of WHO (WHO, 2007), grade 0 defines a thyroid not palpable or visible, grade 1 is a goiter not visibly enlarged when the neck is in normal position and grade 2 goiter is a thyroid that is visibly enlarged when the neck is in a normal position. Another method for measuring goiter is the use of thyroid ultrasonography (Zimmermann, 2008). This is used in areas of

mild iodine deficiency where palpitation of goiter has poor sensitivity and specificity (Zimmermann et al., 2000). The total goiter rate is used to define severity using the following criteria: <5%, iodine sufficiency; 5.0-19.9%, mild deficiency; 20.0-29.9%, moderate deficiency; and >30%, severe deficiency (WHO, 2007).

3) **Urinary iodine Concentration (UIC).** This is an excellent indicator of recent iodine intake as more than 90% of absorbed iodine is excreted by the kidneys (Cavalieri, 1997). This is collected via urine specimens and measured using inductively coupled plasma mass spectroscopy (ICP-MS) or the Sandell-Kolthoff reaction microplate method in which iodine catalyzes the reduction of yellow ceric ammonium sulfate to colorless cerous form in the presence of arsenious acid (Ohashi et al., 2000).Urinary iodine concentration (UIC) can be expressed as a concentration (µg/l) or 24-h excretion (µg/d) and the units are non-interchangeable. Although urine samples are easy to collect in most population groups, it is impractical to collect 24-h samples in population field studies (Rohner et al., 2014). This is the reason why most population iodine studies have UIC measured in spot urine specimens and reported as a median concentration (**Table 2.3**) of a target population since wide day to day variation of iodine intake occur on individual level (Pironi et al., 2015). The NHANES measures UIC to monitor the iodine status among US population aged 6 years and older since 1971 (Lee et al., 2016).

TABLE 2.3 Assessing iodine nutrition at a population level, based on median of UICs

Median UI(µg/l)	Iodine intake	Iodine nutrition
<20	Insufficient	Severe iodine deficiency
20-49	Insufficient	Moderate iodine deficiency
50-99	Insufficient	Mild iodine deficiency
100-199	Adequate	Optimal
200-299	More than adequate	Risk of iodine-induced hyperthyroidism
>300	Excessive	Risk of iodine-induced hyperthyroidism, autoimmune thyroid disease
Pregnant women		
<150	Insufficient	
150-249	Adequate	
250-499	More than adequate	
≥ 500	Excessive	
Lactating women[a]		
< 100	Insufficient	
≥ 100	Adequate	
Children less than 2 years of age		
< 100	Insufficient	
≥ 100	Adequate	

[a] In lactating women, median urinary iodine for adequate iodine intake are lower than the iodine requirements because of the iodine excreted in breast milk.

(Data from references **Sources:** Zimmermann and Boelaert, 2015; Zimmermann and Crill, 2010; Zimmermann, 2011; World Health Organization (WHO, 2007); UI, Urinary Iodine).

2.9 Roles of Iodine via Thyroid Hormone Synthesis in Growth and Development

2.9.1 Growth

TH plays an essential role in linear growth, skeletal development, bone mass maintenance and efficient fracture healing (Harvey et al., 2002). Research has shown the stimulating effect of T3 in DNA synthesis in osteoblast and other cells essential for linear growth (Kassem et al., 1993). T3 increases the expression of osteoblast differentiation markers including Collagen I, osteocalcin, osteopontin, Alkaline Phosphatase, MMp9, and MMP13 in osteoblasts (Pereira et al., 1999; Gouveia et al., 2001; Varga et al., 2010; Varga et al., 1997; Bonovac and Koren, 2000). Growth arrest characterized with delayed bone formation and mineralization are typical in juvenile hypothyroidism with T4 replacement inducing rapid catch growth (Rivkees et al., 1988). TH also has a positive effect on wound healing and proliferation of cells including bone marrow pro-β cells, pancreatic acinear cells, renal proximal tubular epithelial cells and cultured bovine thyroid cells (Safer et al., 2005; Di Fulvio et al., 2000; Foster et al., 1999; Ohmura et al., 1997; Ledda-Columbano et al., 2005).

Furthermore, TH is a key regulator of both local and endocrine Insulin-like growth factor (IGF-1) action during the prepubertal growth period (Kim and Mohan, 2013). Studies using genetic mouse models deficient in TH reported that serum levels of IGF-1 were reduced by more than 50% compared to wild-type mice because of a decrease in IGF-1 expression in liver and bone (Xing et al., 2012). Daily treatment during the prepubertal growth period (days 5 to 14) in these mice increased IGF-1 expression in both liver and bone, normalizing serum IGF-1. Other researches have also reported increased stimulation of growth upon increase in serum IGF-1 levels as a result of TH administration (O'shea et al., 2005; Lakatos et al., 1993).

In human studies, treatment of Iodine deficiency in school age children increased IGF-1 and improved somatic growth (Zimmermann et al., 2007). In addition, T4 administration increased growth in hypothyroid Colombian children with minimal thyroid dysfunction (Hernandez-Cassis et al., 1995).

2.9.2 Neurodevelopment

TH regulates developmental processes like neurogenesis, myelination, dendrite proliferation and synapse formation during pregnancy (Bernal et al., 2003; Bernal, 2007; Zoeller and Rovet, 2004). Maternal iodine deficiency and the resulting hypothyroxinemia where T4 concentrations are low for the stage of pregnancy is the main cause of endemic neurological cretinism (Williams, 2008). In the absence of general signs of hypothyroidism, profound mental retardation, cerebral spastic diplegia, and squint are symptoms of neurological hypothyroidism caused by low maternal T4 levels (Porterfield and Hendrich, 1993).

There are three stages of TH-dependent neurological development (Williams 2008). The first stage occurs before the onset of TH synthesis by the fetus which occurs 16-20weeks post conception in humans or by embryonic day E17.5-18 in rats. In this period, TH is solely sourced from maternally synthesized hormone (de Escobar et al., 2004; Morreale et al., 2004; Obregon et al., 2007; Morreale et al., 2000) which influences neuronal proliferation and migration of neurons in the cerebral cortex, hippocampus and medial ganglionic eminence (Narayanan and Narayanan, 1985; Lucio et al., 2005; Cuevas et al., 2005; Auso et al., 2004).

In the second stage, the developing fetus derives its supply of thyroid hormones from both the fetus and the mother (de Escobar et al., 2004; Morreale et al., 2004; Obregon et al.,

2007; Morreale et al., 2000). This stage occurs during the remainder of the pregnancy after the onset of fetal thyroid function. Neurogenesis, neuron migration, axonal outgrowth, dendritic branching, synaptogenesis, initiation of glial cell differentiation and migration and onset of myelination are the TH dependent processes in this stage (Bernal et al., 2003; Porterfield and Hendrich, 1993; Morreale et al., 2000).

The third stage occurs in the neonatal and post-natal period when TH derived from the child becomes the main source for the child's brain, and this stage is essential for continuing maturation (Williams, 2008). During this period, migration of granule cells in the hippocampal dentate gyrus and cerebellum, pyramidal cells in the cortex and purkinje cells in the cerebellum are sensitive to the TH (Bernal et al., 2003; Porterfield and Hendrich, 1993; Morreale et al., 2000). Furthermore, TH-dependent gliogenesis and myelination continues in this stage.

During the first trimester of pregnancy, there is an increase in maternal TH production imposed by the embryo to ensure an adequate supply of maternal T4 to the fetus during early TH dependent neurodevelopment (de Escobar et al., 2004; Morreale et al., 2004). The increase need arises due to increased volume of TH distribution in plasma, increased metabolism and turnover in pregnancy, and the effects of estrogen on TH binding proteins (Williams, 2008).

2.10 Classical Iodine Deficiency Disorders (IDD)

Iodine deficiency disorders covers a spectrum of disorders which occur as a consequence of iodine deficiency. They include increased fetal and infant mortality, irreversible mental and neurologic retardation, hypothyroidism, goiter and sub-clinical hypothyroidism (Dunn, 2003; Delange, 2000; Dunn and Dunn, 2000). These disorders could impose educability, impaired

economic productivity, increased child mortality, wasted reproductive effort as well as increased health costs (Dunn, 2003).

2.10.1 Neurologic Deficits/ Cretinism.

The consequences of iodine deficiency during gestation depend on the severity of the hypothyroidism (Zimmermann, 2011). Cretinism occurs as a result of extreme hypothyroidism or severe iodine deficiency *in utero* (Zimmermann, 2011; Dunn, 2003). In 1908, two classic forms of cretinism: - neurologic and myxedematous was described (McCarrison, 1908). Worldwide, neurologic cretinism is the most common form (Chen and Hetzel, 2010) characterized with the following clinical features (Halpern, 1991; DeLong et al., 1985; Zimmermann, 2011):

- Mental retardation
- Defects of hearing and speech
- Squint
- Impaired voluntary motor activity involving spastic diplegia or paresis of the lower limbs.
- Disorders of stance with spastic gait and ataxia.

However, researchers have reported euthyroidism in neurological cretins, but goiter and hypothyroidism are seen in some cases (Zimmermann, 2011).

In myxedematous cretinism, which is a severe or long-standing hypothyroidism, the following features are present:

- Mental retardation
- Dwarfism
- Sexual retardation
- Retarded maturation of body parts
- Skeletal retardation
- Weak abdominal muscles

- Poor bowel function
- Myxedema
- Dry, thickened skin
- Sparseness of hair and nails
- Deep hoarse voice

Although cretinism is the expression of abnormalities in development caused by iodine deficiency (ID), cognitive deficits associated with ID are not limited to remote, severely iodine deficient areas (Zimmermann, 2011). In areas of iodine sufficiency, two prospective case-control studies on impaired maternal thyroid function have reported developmental impairment in offspring of affected mothers. In a study by Pop et al., 1999, impaired infant development to 2years of age were reported in women with hypothyroxinemia (free T4 below the tenth percentile at 12weeks gestation) compared to controls. In another study by Haddow et al., 1999, children 7-9years from mothers with normal thyroid function during pregnancy had intelligence quotient (IQ) scores 4 points higher compared to children of mothers with subclinical hypothyroidism during pregnancy (an increased TSH in the 2^{nd} trimester). Furthermore, a metanalyses of 18 studies using different test concluded that iodine deficiency had cost individuals an average of 12.5 IQ points (Bleichrodt and Born, 1994). A study by van Mil et al., 2012 reported that low maternal urinary iodine during early pregnancy is associated with impaired executive functioning in children. Analyses performed by these authors showed that children of mothers with low UIC showed higher scores on the problem scales of inhibition [β = 0.05 (95% CI: 0.01, 0.10), P = 0.03] and working memory [β = 0.07 (95% CI: 0.02, 0.12), P = 0.003].

Different clinical trials have demonstrated the prevention of cretinism via iodine treatment in areas of severe ID (Pharoah and Connolly, 1987; Moreno-Reyes et al., 1994). In a trial in Papua New Guinea, Iodine supplementation was associated with a significant reduction in

the prevalence of endemic cretinism with relative risk (95% CI) of 0.27 (0.12, 0.60) at 4 years of age and 0.17 (0.05, 0.58) at 10 years of age. A long-term follow-up by the authors on a small sub-sample of non-cretinous children at 11 and 15years of age (Pharoah and Connolly, 1991) found no significant differences in motor and cognitive function between the children born to supplemented families and controls.

2.10.2 Infant Mortality

Iodine deficiency increases neonatal mortality (Dunn and Delange, 2001. Experiments conducted throughout the world have demonstrated the efficacy of iodine supplementation in attenuating infant death associated with poor iodine status. For example, in western China, infant mortality decreased to half the average of the previous years upon addition of potassium iodate (KI3) to irrigation water (DeLong et al., 1997). Moreover, odds of neonatal death were reduced by about 65% in comparison with untreated villages. In Zaire, iodine oil given intramuscularly to pregnant women at 28 weeks of gestation (Moreno-Reyes et al., 1994) produced remarkable results. In severely iodine deficient women, the infant mortality rate (IMR) in infants of treated vs. untreated mothers was 113/1000 and 243/1000 births respectively, while in women with mild and moderate ID, the IMR with and without treatment was 146/1000 and 204/1000 births respectively. Oral iodized oil was also shown to be effective in Algeria where rates of still and premature birth were significantly lowered among women given the oil 1-3months before conception or during pregnancy compared with untreated women (Chaouki and Benmiloud, 1994).

2.10.3 Iodine Deficiency Goiter

Although not the most dangerous, goiter is the most obvious manifestation of iodine deficiency (Dunn, 2003). A prevalence of more than 5% in a community suggest iodine deficiency as the causative agent (Dunn, 2003). The increased TSH secretion by the pituitary action causes a diffuse enlargement of the thyroid signaling the thyroid working under pressure. Once someone has been iodine deficient for several years, the thyroid may never return entirely to a normal size even after adequate iodine supplementation (Dunn and Delange, 2001). Before salt iodization in the 1920s, the USA and Canada including the Appalachians recorded 26% to 70% of school age children with goiter (Kelly and Snedden, 1960; Pretell et al., 2017). However, this has reduced over the years with few cases (Pretell et al., 2017).

Additionally, excessive iodine intake is considered risk factor for goiter development (Venturi and Venturi, 2009; Hurrell, 1997; Zimmermann et al., 2008; Teng et al., 2006). This occur due to failure to escape from the Wolf-Chaikoff effect or due to persistent stimulation by thyroid stimulating antibodies that keep the NIS activated (Farebrother et al., 2019). In addition, this stimulation could increase lymphocytic infiltration such as Hashimoto's causing an increase in thyroid size, chronic inflammation of the thyroid gland and subsequent hypothyroidism in iodine sufficient areas (Zimmermann and Boelaert, 2015; Luo et al., 2014; Farebrother et al., 2019).

2.11 Iodine-induced Hyperthyroidism

Iodine-induced hyperthyroidism also known as Jod-Basedow effect is frequently observed following iodine supplementation in a very low iodine intake areas where the risk of

nodular goiter is increased (Lauberg et al., 2010; Farebrother et al., 2019). Under iodine deficient conditions for a long period, TSH hyperstimulation may occur as an adaptive response. This can promote autonomous growth and function of thyrocyte clusters possibly due to mutation promoted by H2O2(Lauberg et al., 2001; Lauberg et al., 2010). With an increase in iodine exposure via supplementation, these nodules may escape the control of TSH and autonomously over-produce TH, causing hyperthyroidism (Farebrother et al., 2019). Even modest increases in iodine intake < 300µg/day can trigger this phenomenon after a long-term deficiency (Farebrother et al., 2019). The degree of effect depends on longevity and severity of iodine deficiency and the degree of increased exposure to iodine (Stanbury et al., 1998). Older persons with long exposure to iodine deficiency and living in an iodine deficient area are proposed risk factors for Jod-Basedow effect (Burgi, 2010; Lauberg et al., 1991; Prete et al., 2015; Roti et al., 2001).

Grave disease (GD) is the most common cause of hyperthyroidism in iodine sufficient regions affecting 0.5% of the population particularly younger adults (Brent, 2008; Girgis et al., 2011; De Leo et al., 2016). GD is due to abnormal stimulation of TSH receptor by IgG antibodies on thyroid cells (Farebrother, 2019). The mimicry of TSH stimulates increased TH liberation and thyroid hyperplasia causing diffuse goiter to be present (De Leo et al., 2016). Genetic proponent that induces sensitivity to environmental factors including smoking, stress, irradiation, infection, iodine overload and iodine-containing drug use (e.g., amiodarone) are considered risk factors for GD development (Brent, 2008; De Leo et al., 2016; Davies, 2013; Marino et al., 2015; Struja et al., 2017). Thyroid auto immunity is considered a common outcome of excessive iodine consumption (Lauberg et al., 2010; Flores-Rebollar et al., 2015; Luo et al., 2014; Prete et al., 2015; Ferrari et al., 2017). Other predisposing factors are underlying autoimmune thyroiditis (AT), treatment of the thyroid with radioactive iodine and

history of external thyroid irradiation, previous thyroidectomy, postpartum thyroiditis and some medications such as lithium which interfere with iodine organification and TH release (Markou et al., 2001). Risk of developing AT is higher in females (Ferrari et al., 2017; Pedersen et al., 2003; Hollowell et al., 2002) and Caucasian populations (Hollowell et al., 2002) due to genetic predispositions (Ferrari et al., 2017). Older adults ≥ 45years of age are also considered at risk for AT development due to observed peak positive antibodies at this stage (Ferrari et al., 2017).

Furthermore, a link between thyroid cancer and excess iodine intake has been proposed (Blomberg et al., 2012) possibly due to increased oxidative DNA damage (Prete et al., 2015) though there are few data to support this theory (Farebrother et al., 2019). However, Cao et al., 2017 (Cao et al., 2017) reported that an iodine intake > 300µg/day decreased the risk of thyroid cancer (OR 0.74; 95% CI: 0.6-0.9).

2.12 Roles of Iodine via Thyroid Hormone in Metabolism

2.12.1 Thermogenesis

2.12.1.1 Basal Metabolic Rate (BMR). TH is a key regulator of BMR although the targets are not clearly established (Kim, 2008; Mullur et al., 2014). BMR correlates positively with lean body mass (Johnstone et al., 2005) and TH levels (Danforth and Burger, 1984; Silva, 2003). Moreover, patients with hypothyroidism and hyperthyroidism present clinical symptoms of cold and heat intolerance respectively (Mullur et al., 2014). TH stimulates BMR through the generation and maintenance of ion gradients (Haber and Loeb, 1986; Silva, 2006) and increase in ATP production (Freake et al., 1989). TH stimulates the ion gradient directly or in directly, first being the $NA^{+/}K^{+}$ gradient across the cell membrane (Mullur et al., 2014). It does this by altering

the levels of Na^+ within the cell and K outside of the cell, thus requiring ATP consumption in the form of Na^+-K^+-ATPase, although research has shown that this effect has more impact on BMR in hyperthyroidism than in euthyroid or hypothyroid individuals (Clausen et al., 1991; Edelman and Ismail-Beigi, 1974; Ismail-Beigi, 1992). The Ca^{2+} gradient between the cytoplasm and sarcoplasmic reticulum is also stimulated by TH. TH regulates the expression of the sarcoplasmic /endoplasmic reticulum Ca^{2+}-dependent ATPase (SERCA) in skeletal muscle (Simonides et al., 1996; Simonides et al., 2001; Zurlo et al., 1990) which produces heat during ATP hydrolysis (De Meis, 2001). TH also increases the amount and activity of ryanodine receptors in heart and skeletal muscle, causing a Ca^{2+} efflux into the cytosol, thereby requiring more ATP to return the Ca^{2+} to the sarcoplasmic reticulum (Mullur et al., 2014; Jiang et al., 2000).

TH maintains BMR by uncoupling oxidative phosphorylation in the mitochondria (Hafner et al., 1988) or reducing the activity of the shuttle molecules that transfer reducing equivalents into the mitochondrion (Fahien et al., 1999; Harper and Seifert, 2008). In skeletal muscle, the leak of protons through the mitochondrial inner membrane is increased by TH to stimulate more oxidation to maintain ATP synthesis since the proton-motive force during ATP production is compromised (Mullur et al., 2014). The presence of uncoupling protein (UCP) 2 and 3 were initially suggested as mediators of the TH-stimulated proton leak. However, investigation reports that TH treatment produced upregulation of UCP2 and UCP3 but had no association with changes in the proton gradient in human muscle (Barbe et al., 2001). T3 also regulates the mitochondrial glycerol-3-phosphate dehydrogenase (mGPD) induction, an enzyme that contribute to ATP generation by transfer of reducing equivalents generated in the cytoplasm into the mitochondria membrane (Mullur et al., 2014). In a research by DosSantos et al., 2003,

transgenic mice lacking in mGDP even with higher levels of T4 and T3, had impaired ability to maintain core body temperature, consistent with a defect in thermogenesis (DonsSantos et al., 2003). A research by Flandin et al., 2009 reports that T3 treatment of beta 1, 2 and 3 adrenergic receptor knock-out mice which were cold intolerant resulted in maintenance of body temperature during cold exposure (Flandin et al., 2009).

2.12.1.2 Facultative Thermogenesis. Strong evidence describes the important role of TH in the facultative thermogenesis (non-shivering) of homeothermic species to maintain core body temperature after cold exposure and energy expenditure increase after eating (Mullur et al., 2014; Silva, 2003). The primary site of facultative thermogenesis in rodents is in the brown adipose tissue (BAT) (Cannon and Nedergaard, 2004). Research has shown that the absence of TH in facultative thermogenesis causes a reduction in thermogenic response of BAT to colder environments (Seydoux et al., 1982; Bianco and Silva, 1987). Further investigation revealed that hypothyroid rodents develop hypothermia with cold exposure and treatment with T4 reverses this via induction of BAT activity (Carvalho et al., 1991). UCP1 expression is required for BAT thermogenesis and this is synergistically regulated by both norepinephrine (NE) and TH. T3 increases UCP1 expression by 2-fold, however in combination with NE, there could be a 20-fold induction of UCP1 (Bianco et al., 1988). The UCP1 gene contains several cAMP response elements (CRE) that enhance the responsiveness of adjacent thyroid response elements (TREs) to T3 (Silva and Rabelo, 1997). The presence of D2 required for the local conversion of T4 to T3 in BAT is also essential for facultative thermogenesis (De Jesus et al., 2001; Ellis, 2006). This enzyme is stimulated by the sympathetic nervous system (SNS) when BAT thermogenesis is needed increasing the intracellular concentration of T3 to receptor saturating levels (Silva, 2003). This high level of T3 through the conversion of T4 by D2 are needed to unleash the thermogenic

potential of BAT by mobilization of tissue lipid which are fuel for heat production (Bianco and Silva, 1987a; Bianco and Silva, 1987b). In hypothyroidism, increased D2 activity increases sympathetic stimulation of BAT to protect T3 content of BAT. However, in severe hypothyroidism, T3 content of BAT gets depleted and leads to low tolerance for cold (Carvalho et al., 1991).

2.12.1.3 Regulation of Body Weight. There is evidence that TH modulates numerous cellular processes relevant to resting energy expenditure (REE) (Reinehr, 2010; Danforth & Burger, 1984; Onur et al., 2005). In healthy individuals, slight variations in serum TSH, were associated with body weight change in men and women (Fox et al., 2008; Knudsen et al., 2005). Results further show that individuals with serum TSH levels in lower quantiles have lower BMI and at upper quantiles, a higher BMI. A positive correlation has been shown between weight gain and a progressive increase in serum TSH over a 5-year period and elevated concentrations of TSH (usually below 10iu/L) were noted in 25% of the obese subjects studied (Knudsen et al., 2005).

A decrease in T4 concentration in obese humans with TSH-levels hints to hypothyroidism (Reinehr, 2010). The treatment of hypothyroid individual with T4 in a recent study was associated with a reduction in body weight and an increase in REE although fat mass remained unchanged (Karmisholt et al., 2011). In an investigation where hypothyroid patients were treated with T3 monotherapy, there was significant weight loss and reduction in total cholesterol and apolipoprotein B (Celi et al., 2011). However, there was no significant decrease in fat mass and no significant change in REE associated with the weight loss. The authors postulated that an increase in metabolic rate was likely attributable to the weight loss in the T3

therapy. In a separate examination of body composition in hyperthyroidism, weight loss associated with treatment was due to loss of both fat and lean body mass (Lonn et al., 1998).

2.12.2 Lipid Transport and Metabolism.

In 1900, Von Noorden working in Vienna, recognized that the thyroid plays a role in the development of "fatty disease" (Duntas and Brenta, 2012). In 1918, researchers reported that blood cholesterol is related to "the glands of internal secretion" particularly the adrenals and thyroid. In addition, studies in the early 1930s revealed the association of cholesterol to thyroid function and disease (Von, 1900; Luden,1918; Epstein and Lande, 1922).

Cholesterol is generated by the reduction of mevalonate by HMG-COa reductase (rate-limiting enzyme) through hydrolysis of acetyl coenzyme A (CoA) and acetoacetyl-CoA that forms 3-hydroxy-3-methyl glutaryl-CoA (HMG-CoA). After, generation, cholesterol is transported within the blood by lipoproteins, classified by increasing density as chylomicrons, very low-density lipoprotein (VLDL), intermediate density lipoprotein (IDL), low density lipoprotein (LDL) or high-density lipoprotein (HDL) (Duntas and Brenta, 2012). Cardioprotective HDL is subdivided into HDL2 (lipid content, 59-67%) and HDL3 (4-44%) (Duntas, 2005).

The major pathway for regulation of cholesterol synthesis by TH is through the stimulation of the LDL-R gene resulting in increased uptake of cholesterol and enhanced cholesterol synthesis (Lopez et al., 2007). This is a major pathway of T4-mediated cholesterol-lowering after TH replacement therapy of patients with hypothyroidism (Klein and Danzi, 2007). SREBP-2 (Sterol regulatory element binding protein-2) whose gene expression is induced by TH in turn modulates LDL-receptor expression which regulates cholesterol synthesis (Espenshade

and Hughes, 2007). SREBP-2, a transcription factor bound to SCAP (SREBP-cleavage activating protein) and INSIg1 (Insulin-Induced gene 1 after cleavage by S1P (sphingosine-1-phosphate) and S2P, migrates to the nucleus and acts as a transcription factor to bind to the sterol regulatory element, which stimulates transcription of LDL receptor and HMG-CoA reductase genes (Duntas and Brenta, 2012). Shin and Osborne (2003) reported that hypothyroid rats had suppressed SREBP-2 mRNA but was reversed when T3 levels are restored (Shin and Osborne, 2003). The same researchers also reported a reversal of hypercholesterolemia when T3 levels were restored in the hypothyroid rats (Shin and Osborne, 2003).

Furthermore, TH also reduces blood cholesterol through non-LDL receptor-mediated pathways. LDL-gene knockout mice with hypercholesterolemia were treated with high dose T3; the subsequent reduction in LDL-C was linked to reductions in apolipoprotein (apo) B48 and apoB11. This finding suggests another mechanism for T3 cholesterol lowering actions through its upregulation of apolipoprotein AV gene (APOAV), a major determinant of triglyceride metabolism (Prieur et al., 2005). Increased serum triglycerides have opposing effects such as proatherogenic changes in lipoprotein including the generation of small, dense LDL and reduction of cardioprotective HDL (Griffin and Zampelas, 1995; Mason et al., 1930).

2.12.2.1 Hepatic Clearance and Bile Acid Synthesis. TH induces accelerated clearance of cholesterol by the liver through increase of HDL receptor also known as scavenger receptor B1 (Johansson et al., 2005) and increase in bile synthesis via the up-regulation of cholesterol 7 alpha-hydroxylase (CYP7a1), the rate limiting step in bile acid synthesis (Day et al., 1989). The increase in bile acids flow causes a depletion of the intrahepatic cholesterol pool which in turn causes an increase in cholesterol synthesis in the liver and hepatic uptake of cholesterol from the circulation in order to create balance in hepatic cholesterol levels (Duntas and Brenta, 2012).

Additionally, increase in bile acid flow causes bile acid to bind to TGR5 and stimulate D2 expression which increases energy expenditure and promotes resistance to diet-induced obesity (Thomas et al., 2008; Watanabe et al., 2006). A recent clinical study in both healthy and cirrhotic subjects revealed that bile acid synthesis correlated positively with energy expenditure and serum TSH decreased in both groups postprandially (Ockenga et al.,2012).

2.12.2.2 Fatty Acid Metabolism. TH has a direct action on lipolysis and lipogenesis with the latter considered compensatory measure used to restore fat stores (Oppenheimer et al., 1991). A rat study receiving T3 treatment, reported that TH-induced lipogenesis is primarily to maintain fat loss due to TH-induced lipolysis (Oppenheimer et al., 1991). They also noted that fatty acids produced from TH-induced lipolysis are the substrate for increase in thermogenesis. T3 regulation of this metabolic pathway is influenced by nutritional status, ligand binding, nuclear receptor crosstalk and competition for RXR heterodimers (Liu and Brent, 2010). TH induces the transcription of acetyl CoA Carboxylase (ACC)-1 which generates malonyl CoA from acetyl CoA (Huang and Freake, 1998). Furthermore, lipophagy, the mobilization of lipid droplets into the hepatocyte has been shown to be T3 regulated (Singh et al., 2009). Interestingly, impairment of this process is associated with hepatic steatosis and IR (Yang et al., 2010).

2.12.3 Blood Glucose Control and Carbohydrate Metabolism

2.12.3.1 Gluconeogenesis, Glucose Uptake and Insulin Sensitivity. Thyroid hormones have several tissue-specific effects on blood glucose control. T3 controls insulin secretion, gluconeogenesis, and glucose uptake acting differently in the liver, skeletal muscle and adipose tissue which are the main targets of insulin action (Brent, 2012; Potenza et al., 2009). In the liver,

TH has insulin antagonist effects. Hepatic glucose output is increased by TH through an increased hepatic expression of glucose transporter-2 (GLUT-2). TH also stimulate endogenous production of glucose via increase in gluconeogenesis and glycogenolysis which is responsible for the decrease of liver sensitivity to insulin (Duntas et al., 2011; Feng et al., 2000). A study by Singh and Synder (1978) reported an increase in alanine transport into hepatocytes after treatment with T4 (Singh and Synder, 1978). This increased the conversion of alanine into glucose and the production of metabolic intermediate of the gluconeogenic pathway. The synthesis of PEPCK (Phosphoenolpyruvate carboxykinase), the rate limiting step of GNG and increase of G6P mRNA expression is shown to be regulated by TH (Park et al., 1995; Park et al., 1999). Hepatic PEPCK (Phosphoenolpyruvate carboxykinase) mRNA is stimulated 3.5fold and resistant to insulin suppression of hepatic glucose production in thyrotoxic rats compared with euthyroid rats (Klieverik et al., 2008).

The sympathetic pathway connecting the paraventricular hypothalamus to the liver is centrally controlled by T3 to modulate hepatic glucose production and insulin sensitivity (Klieverik et al., 2009). T3 administration in hypothalamic PVN increase hepatic production of glucose independent of plasma T3, insulin, glucagon and corticosterone. TH facilitates gluconeogenic effect of epinephrine and glucagon by stimulating β-2 adrenergic receptor mRNA and inhibiting inhibitory G protein RNA of the adenylate cyclase cascade (Feng et al., 1991).

In the skeletal and adipose tissue, TH works in synergy to increase both basal and insulin-stimulated glucose transport (Weinstein et al., 1994). T3 modulates GLUT4, adenosine monophosphate-activated protein kinase, and acetyl coenzyme A carboxylase mRNA and protein expression (Crunkhorn and Patti, 2008). An increase in insulin dependent GLUT4 mediated glucose uptake within 30 minutes without interfering with other transporters such as GLUT1 and

GLUT3 have been reported in hypothyroid rats treated with T3 (Teixeira et al., 2012). T3 stimulates normal adipocyte-myocyte crosstalk by the release of adipokines by adipose tissue to modulate insulin sensitivity of skeletal muscle and the production of myokines by skeletal muscle to affect the adipose tissue (Havekes and Sauerwein, 2010). However, both hypothyroidism and hyperthyroidism can contribute to IR through its interference with normal adipocyte-myocyte crosstalk (Havekes and Sauerwein, 2010).

2.12.3.2 Insulin Production and Action. T3 is required for the transition of pancreatic islets to glucose responsive insulin-secreting cells (Mullur et al., 2014). TH has been shown to promote the proliferation of pancreatic islet cells in a culture (Furuya et al., 2006). In streptozotocin (STZ)-induced diabetic rats, T3 treatment prevents islet deterioration, maintains islet structure, size and consistency (Verga Falzacappa et al., 2011). Further, T3 induces these anti-deteriorative effects via nongenomic activation of the AKT signaling pathway. T3 also promotes the proliferation of pancreatic islet cells (Fukuchi et al., 2002). In a study using Zucker rats, T3 treatment reversed hyperinsulinemia in obese animals (Torrance et al., 1997).

2.13 Subclinical Hypothyroidism and Conditions Associated with MetS

SCH, also called mild hypothyroidism or compensated hypothyroidism, is a condition in which there are small elevations in TSH with normal circulating levels of thyroid hormones (Hueston and Pearson, 2004; Zimmermann, 2003; Chopra et al., 1975, Delange et al., 1972). This condition is more common in the elderly with higher prevalence in women compared to men (Sawin et al., 1985; Tunbridge et al., 1977). In younger persons <65yrs, the overall prevalence of the disorder is about 17% in women and 7% in men (Danese et al., 2000). Because

one-third of the global population is affected by iodine deficiency (Andersson et al., 2012), iodine deficiency remains a common cause of SCH worldwide (Papi et al., 2007).

The diagnosis of MetS requires a combination of "metabolic health" assessment criteria including measurements of body weight/composition, blood pressure, systemic inflammation, serum lipid profile, and IR (Phillips & Perry 2013). As previously described, MetS is a significant health problem as it increases the risk of the development of chronic diseases such as CVD and T2D; its prevalence in Western countries is ~20% (Phillips & Perry 2013). There is a growing body of evidence for a connection between SCH and indicators of metabolic health.

SCH is associated with an increased risk of elevated cholesterol levels (Vierhapper et al., 2000; Canaris et al., 2000; Pirich et al., 2000), IR and subclinical inflammation (Pearce, 2012; Biondi and Cooper, 2008), dyslipidemia (Asvold et al., 2007), higher BMI (Knudsen et al., 2005) and mortality from coronary artery disease (Asvold et al., 2008; Redford and Vaidya, 2017).

In a study of 2799 elderly Black and Caucasian subjects, serum TSH values above 5.5mIU/l were linked with an average 9 mg/dl elevation in total cholesterol (Kanaya et al., 2002). In Colorado, a statewide health fair study of 25,862 participants reported elevated levels of total cholesterol, triglyceride and LDL-C levels in SCH subjects compared with euthyroid subjects (Canaris et al., 2000). In Australia, serum TSH was positively correlated with total cholesterol, triglycerides and LDL-C although no associations were observed between serum TSH and HDL-C (Walsh et al., 2005). Among 1534 Chinese adults studied, those with subclinical hypothyroidism had higher triglycerides and lower HDL-C than euthyroid individuals (Lai et al., 2011). In a cohort study of 2771 euthyroid Hispanics, T4 was positively associated with serum HDL-C and serum TSH was positively correlated with total cholesterol and triglyceride after adjustment for age, gender and body mass index (Garduno-Garcia et al., 2010).

Among 30,656 euthyroid individuals in the HUNT study, serum TSH was positively associated with total cholesterol, LDL-C and triglycerides (Asvold et al., 2007). A randomized control trial by Herter-Aeberli et al., 2015 in iodine deficient women reported a decrease in hypercholesterolemia after iodine supplementation with oral KI tablets (Herter-Aeberli et al., 2015). In a recent study by Lee et al., 2016 using NHANES (National Health and Nutrition Examination Survey), low UIC was associated with increased odds for dyslipidemia.

However, some observations of the serum lipid levels in patients with SCH have been inconsistent with the reports above (Pearce, 2012). In a cross-sectional study of 7000 thyroid clinic patients, no significant differences were found in serum total cholesterol, LDL-C, HDL-C or triglyceride levels between SCH patients and euthyroid control group (Vierhapper et al., 2000). Among 8586 adults over age 40yrs from NHANES III database, SCH (serum TSH of 6.7 to 14.99mIU/L) was not associated with alterations in total cholesterol, LDL-C, triglycerides or HDL-C after adjustment for age, race, sex and use of lipid lowering drugs (Hueston and Pearson, 2004).

A few prospective studies have reported an increased risk of diabetes and IR in hypothyroid patients (Gronich et al., 2015; Thvilum et al., 2013). A study by Gronich et al., 2015 showed that within 59,597 participants studied, hypothyroidism and SCH carried an increased risk for diabetes [Relative risk (RR 1.53; 95% CI: 1.31-1.79) and 1.75 (1.40-2.18), respectively]. In the same study, diabetes risk indicators were resolved in hypothyroid patients treated with TH replacement. A 6-year observational Danish cohort of 2822 hypothyroid individuals showed a significant risk of being diagnosed with diabetes [Hazard ratio (HR 1.40; 95% CI: 1.11-1.77); cardiovascular diseases (HR 1.36; 95% CI: 1.15-1.60) and lung diseases (HR 1.51; 95% CI: 1.30-1.75) (Thvilum et al., 2013). Among 8452 participants (mean age 65years) in the Rotterdam

prospective population-based study, higher TSH levels and lower freeT4 (FT4) levels were associated with an increased risk of diabetes and progression from prediabetes to diabetes ((HR 1.32; 95% CI: 1.06-1.64 for TSH and HR 0.91; 95% CI: 0.86-0.97 for FT4) (Chaker et al., 2016).

Investigations have also sought to determine the at-risk population for thyroid dysfunction in T2D. These inquiries have indeed revealed that among those with T2D, female sex, older age, obesity, and hospitalization are associated with an increased risk for thyroid dysfunction (Chubb et al., 2005; Al-Geffari et al., 2013; Diez and Iglesias, 2012; Chen et al., 2010; Song et al., 2017).

2.13.1 Iodine as a Threshold Nutrient

Iodine is critically important for thyroid health (Zimmermann, 2009) and metabolic health (Biondi et al., 2019). Iodine functions as a threshold nutrient, that is, body iodine levels increase as iodine intake increase. However, when it gets to a threshold value, no further intake alter retention. In most individuals, iodine intake below 100µg/L causes a progressive reduction in renal iodide excretion although TSH secretion and release of T3 into the blood is augmented (Abrams and Larsen, 1973). However, iodine intake below the threshold of 50µg/L causes a depletion of iodine content of the thyroid and many individuals may develop notable disorders associated with iodine deficiency (Delange, 2000). The consideration of this threshold is important when factored into the design and evaluation of studies to test for the role of iodine when various biomarkers such as insulin resistance (FBG, HbA1c, HOMA-IR) are used as outcome measures.

2.14 Summary

- Iodine is an essential element necessary for thyroid hormone production.
- Iodine intake within the U.S. population has declined in recent years.
- Mild iodine deficiency increases the risk of inadequate thyroid hormone production and there is growing evidence that sub-clinical hypothyroidism may give rise to outcomes disruptive to metabolic health.
- Metabolic syndrome, characterized by obesity, hypertension, altered blood lipids, and IR, is a significant health problem as it increases the risk of the development of chronic diseases such as cardiovascular disease and type 2 diabetes.
- There is a growing body of evidence for a connection between subclinical hypothyroidism and indicators of metabolic health.
- A few studies have explored the relationship between iodine status (as measured by urinary iodine concentrations) and dyslipidemia; and there is one study on the association between thyroid hormone status and markers of insulin resistance.
- However, no study to my knowledge has assessed the association between iodine status (urinary iodine concentrations) and markers of insulin resistance. This encompasses the aim of the study.

CHAPTER 3
METHODOLOGY

3.1 Data Collection: NHANES

NHANES is a cross-sectional examination survey conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). NHANES survey is based on a complex, stratified, multistage and probability cluster designed to obtain nationally representative samples of civilian, noninstitutionalized residents in the US (NCHS, 2019). NHANES consists of interviews, laboratory tests and physical examinations administered by highly trained staff (CDC, 2019). The protocols used for data in NHANES are approved by the NCHS Research Ethics Review Board and all subjects ≥ 18years give informed consent and participate voluntarily while children and adolescents aged 7 to 17years provide documented assent and parental permission (CDC, 2019). Detailed descriptions of survey plan and design have been previously provided in the NHANES analytic guidelines (NCHS, 2019).

3.2 Sample Population

NHANES became a continuous survey in 1999 with data collected in every two-year cycle. In this study, NHANES cycle (2011-2012) was used and us adults (≥ 20years) who participated in this cycle and have urinary iodine information will be focused on. From the NHANES (2011-2012) cycle data set, physical examination, demographic questionnaire and laboratory sections will be merged using the unique number sequence for each respondent. The total number of respondents for the cycle is 9756. With the research focus on iodine, there were 2594 respondents including missing values in the iodine population representing ages (6-150 years) which represent one-third of the sample. Exclusion criteria include population with

thyroid disorders, cancer, diabetes, pregnant women, populations < 20years of age. After the exclusion, the final sample size of 1286 comprising of adults ≥ 20years were used for analysis in the study described herein **(Figure 3.1)**.

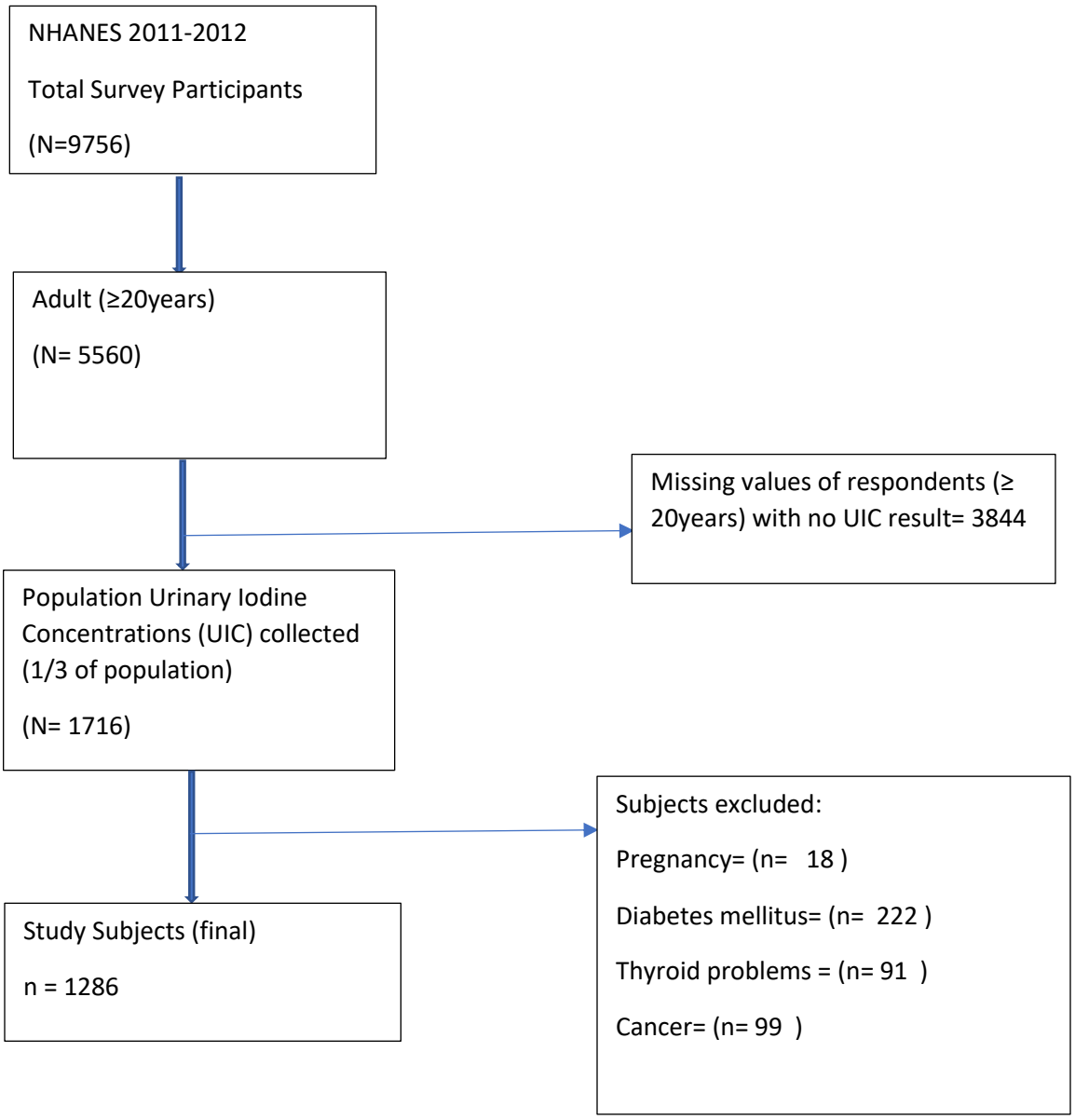


FIGURE 3.1 Flow diagram of subject inclusion

3.3 Measurements Included in Analyses (from NHANES Methods)

3.3.1 Iodine Status

One-third of the sample population aged 6years and older were selected for UIC measurement to represent the U.S. population in NHANES. Spot urine specimens were collected from participants in the MEC (Mobile Examination Center) and assessed using an Inductively Coupled Plasma Mass Spectrometer with Dynamic Reaction Cell Technology (ELAN DRC II) (PerkinElmer, Norwalk, CT, USA) (CDC, 2019; PerkinElmer, 2019). To examine the association of UIC and insulin resistance, the participants included in the study were divided into 2 groups according to UIC distribution and < 100µg/L of them as having low UIC. Insulin resistance were compared between two subgroups (below vs above 100µg/L UIC groups) according to statistical methods previously used by Zou et al., 2015.

3.3.2 Measures of Insulin Resistance

3.3.2.1 Glycated hemoglobin A1C (HbA1c). HbA1c were measured in a full sample to reflect plasma glucose for the previous 120 days. Glycohemoglobin measurements were performed on the A1c G7 HPLC Glycohemoglobin Analyzer (Tosoh Medics, Inc., 347 Oyster Pt. Blvd., Suite 201, So. San Francisco, Ca 94080.). The analyzer integrates and reduces the raw data, and then calculates the relative percentages of each hemoglobin fraction. (<5.5%, 5.5–6.4%, and ≥6.5% represent normal, pre-diabetic and high HbA1c respectively based on WHO (WHO, 2011));

3.3.2.2 Fasting blood glucose (FBG). Fasting glucose blood tests were measured in a fasting subsample (half sample) of persons 12 years and older (n = 2881). Participants who were

examined had their blood drawn in the morning after a 9 hour fast and had their FBG recorded in mmol/L after analyses.

3.3.2.3 Fasting Insulin. Fasting insulin were measured in a fasting subsample (half sample) of persons 12years and older (n= 2881) after a 9 hour fast. This was measured using the Elecsys 2010 Insulin chemiluminescent "sandwich" immunoassay which employs two monoclonal antibodies which are specific for human insulin.

3.3.2.4 HOMA-IR. The homeostatic model assessment (HOMA) was used to quantify IR (Matthews et al., 1985; Wang et al., 2018). Using fasting insulin and glucose values, IR was calculated as shown below and recorded in μU/mL (Matthews et al., 1985; Wang et al., 2018).

HOMA-IR= fasting insulin (μU/mL) * fasting glucose (mmol/L) / 22.5

3.4 Covariates

The NHANES included information collected on the sociodemographic through interviews administered by trained interviewers. In this study, variables included in the statistical analytic models will be sex (men and women); age (20-39, 40-59, >60years); race/ ethnicity [non-Hispanic white (NHW) , non-Hispanic black (NHB), Mexican American, non-Hispanic Asian (NHA), other Hispanic and Other Race - Including multi-racial grouped into four; NHW, NHB, NHA and Hispanics (comprises of Mexican American, other Hispanics and other race)]; Education (less than high school, high school, more than high school); BMI (underweight, < 18.5kg/m2; normal, 18.5 to < 25kg/m2; overweight, 25 to < 30kg/m2, and obese, > 30kg/m2); Waist circumference (<102cm and >120cm (men); <88cm and > 88cm (women) Iodine containing Supplement-use (Yes and No); Poverty income ratio (Low 0 to < 1.85, Medium 1.85 to < 3.5, High ≥ 3.5); Smoking (using serum cotinine concentrations) (low < 0.015ng/ml,

Medium 0.015 - < 10ng/ml, High ≥ 10ng/ml); Alcohol Consumption (None, > 0 to < 1 drink/day, 1 to 2 drinks/ day, ≥ 2 drinks/day); Physical Activity (No activity, 0 to < 500 MET-min/week, 500 to < 1000 MET-min/week, ≥ 1000 MET-min/week). Where MET is Metabolic Equivalent of Task.

3.5 Statistical Analyses

All statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC). To account for complex survey design, survey nonresponse, and planned oversampling, we used SURVEY procedure which include sample weight, stratum (SDMVSTRA), and primary sampling unit (SDMVPSU) as recommended by NCHS for the NHANES analysis. Chi-square goodness of fit test was performed to investigate the associations between UIC and categorical covariates. Estimates for mUIC with 95% confidence interval were calculated for covariates. Least significance difference (LSD) was used to test for differences in IR biomarkers (HOMA-IR, FBG, insulin, HbA1c) by covariates using linear regression (x= covariate; y= IR biomarker). IR biomarkers were compared between the two UIC groups (i.e. Low vs. Normal) using bivariate analysis. Multiple logistic regression was used to analyze risk for abnormal IR values (FBG ≥5.6mmol/L; insulin >9 mU/ml; HbA1c ≥5.7%; HOMA-IR ≥2.6) according to UIC groups. Odds ratios (ORs) with 95% confidence intervals (CIs) was calculated in two models for the general population and gender sub-groups (male and female) before (unadjusted) and after controlling for covariates (adjusted). $P < 0.05$ was used to determine statistical significance.

CHAPTER 4
RESULTS

4.1 Socioeconomic and Lifestyle Variables affecting Markers of UIC and IR

From NHANES 2011-2012, 1286 participants were used for final analyses following the inclusion and exclusion criteria. The descriptive statistics on sociodemographic and lifestyle characteristics of the study population categorized by UIC are presented in **Table 4.1**. Four hundred-ninety participants (37.99%) had low UIC, defined as <100µg/L; and 796 (62.01%) had normal UIC, defined as ≥ 100µg/L. The mUIC of the low group was 55.8µg/L (95% CI, 51.6-60.0) compared to 199.6µg/L for the normal group (95% CI, 180.2-218.9). Among the sociodemographic characteristics, only sex and age had significant associations (P =0.0198 and 0.0238, respectively). However, there were no statistically significant associations between the UIC groups and any of the lifestyle characteristics.

4.1.1 Median Urinary Iodine Concentrations by Covariates

The mUIC of the participants was 126.6 µg/L (95% CI, 111.9-141.2); the weighted percentage of individuals with UIC <100 µg/L was 37.99% (**Table 4.2**). To inform subsequent analyses in this study, the effects of each identified covariate on mUIC was calculated. Only sex, age, BMI, waist circumference (women), and iodine-containing supplement use were significant effects on mUICs ($P < 0.05$).

4.1.2 Insulin Resistance Biomarkers by Covariates

To compare this data set with published observations, IR by covariates was determined. Unadjusted IR biomarkers according to sociodemographic and lifestyle characteristics are shown in **Table 4.3**. Age, race, education, PIR (poverty income ratio), smoking, BMI, alcohol use, waist

circumference, and physical activity were significantly associated with the majority of IR biomarkers.

By age, persons ≥ 60years old had higher FBG and HbA1c ($P < 0.001$) compared to other age groups. Across race, NHB had higher insulin, HbA1c and HOMA-IR ($P < 0.001$) compared to ethnic groups. By education, FBG and HbA1c levels were significantly higher ($P < 0.001$) in individuals with education level <high school compared with other education levels. Individuals with low PIR had higher insulin and HOMA-IR ($P < 0.05$) compared to medium and high PIR individuals. By smoking, those with high cotinine levels had significantly greater insulin, HbA1c and HOMA-IR values ($P < 0.05$) compared to those with low or medium cotinine levels. Across BMI, obese individuals had higher IR markers compared with BMI <30 ($P < 0.001$). Both men and women with greater waist circumference (>102cm and >88cm, respectively) had significantly higher IR biomarkers compared to those within normal waist circumference values. Individuals exercising ≥ 1000MET min/week had lower insulin, HbA1c and HOMA-IR ($P < 0.001$) compared to other physical activity groups.

4.2 Association of UIC with Markers of IR

IR measures in men and women according to UIC status groups are shown in **Table 4.4**. None of the measures of IR were significantly different between the UIC groups for either males or females.

IR measures by age for the two UIC groups are shown in **Table 4.5**. None of the measures of IR were significantly different between the UIC groups for all three age groups.

4.3 Estimate the risks of IR by UIC

The unadjusted (OR) and adjusted odds ratios (AOR) with 95% CIs for risk factors of IR by UIC for all participants are described in **Table 4.6**. In the unadjusted and adjusted model, no statistically significant differences in increased risk of elevated measures of IR were found for any of the UIC groups.

The OR and AOR with 95% CIs for risk factors of IR by UIC for males only are described in **Table 4.7**. In the unadjusted model, no statistically significant differences in increased risk of elevated measures of IR were found for any of the UIC groups. Likewise, no significance was found in the adjusted model.

Table 4.8 shows the OR and AOR with 95% CIs for risk factors of IR by UIC for females only. In the unadjusted model, the odds of elevated HbA1c (≥ 5.7%) in the low UIC group is 44% less than the normal UIC group ($P = 0.0208$). However, no other significant findings were seen in other measures of IR.

In the adjusted model, the odds of elevated HOMA-IR in adult females with low UIC is 44% less than adult females in the normal UIC group ($P = 0.0478$). However, compared to females in the normal UIC group, females with low UIC were more likely to have elevated FBG (pre-diabetics), a marker for IR (OR, 1.73; 95% CI, 1.09-2.72) ($P = 0.0211$). The *P-value* for covariates controlled for each insulin resistance profile in adult females are shown in **appendix**.

Table 4.1. Sociodemographic and lifestyle characteristics of study subjects, NHANES 2011-2012[1], overall and by urinary iodine concentration[1]

	Total		Low UIC (<100µg/ L)		Normal UIC (≥100µg/ L)		Chi-Square
	n	*wt'd%*	*n*	*wt'd%*	*n*	*wt'd%*	***P* value[2]**
All	1286	100	490	37.99	796	62.01	
Socio-demographics							
Sex							
Male	666	50.62	235	16.40	431	34.22	0.0015**
Female	620	49.38	255	21.59	365	27.79	
Age							
20 – 39 y	579	44.62	235	17.48	344	27.14	0.0160*
40 – 59 y	424	38.58	175	16.38	249	22.20	
≥ 60 y	283	16.80	80	4.13	203	12.67	
Race							
NHW	429	63.21	164	24.06	265	39.15	0.9865
NHB	338	12.15	128	4.53	210	7.62	
NHA	221	5.80	86	2.27	135	3.53	
Hispanics	298	18.83	112	7.13	186	11.70	
Education							
< High School	278	15.74	103	5.87	175	9.87	0.1321
High School	248	18.91	92	6.14	156	12.77	
>High School	760	65.35	295	25.99	465	39.37	
Poverty Income Ratio[3]							
Low	670	41.08	244	14.31	426	26.77	0.3670
Medium	250	21.84	100	8.71	150	13.13	
High	366	37.08	146	14.97	220	22.11	
Lifestyle Variables							
Smoking (serum cotinine)[4]	410	37.63	149	13.75	261	23.88	0.3520

Low							
Medium	595	40.11	230	14.68	365	25.43	
High	281	22.26	111	9.56	170	12.70	
BMI[5]							
Underweight	46	3.08	22	1.32	24	1.76	0.3296
Normal	418	32.32	173	13.61	245	18.70	
Overweight	412	33.10	151	11.52	261	21.58	
Obese	410	31.50	144	11.54	266	19.96	
Supplement Use[6]							
Yes	217	18.03	68	5.68	149	12.36	0.1056
No	1069	81.97	422	32.31	647	49.65	
Alcohol Use							
None	486	31.27	176	10.94	310	20.32	0.1274
> 0 to 1 drink/day	263	21.34	102	8.34	161	13.01	
>1 to 2 drinks/day	211	19.31	90	9.27	121	10.05	
> 2 drinks/day	326	28.08	122	9.44	204	18.63	
Physical Activity[7]							
None	745	51.64	276	19.93	469	31.71	0.8763
0 to < 500 MET-min/wk	249	22.15	97	8.09	152	14.06	
500 to <1000 MET-min/wk	161	14.09	65	5.61	96	8.48	
≥1000 MET-min/wk	131	12.12	52	4.35	79	7.77	
Waist Circumference							
Men ≤ 102 cm	426	60.85	157	19.75	269	41.10	0.9767
> 102 cm	240	39.15	78	12.64	162	26.50	
Women ≤ 88 cm	260	43.70	119	20.62	141	23.08	0.1804
> 88 cm	360	56.30	136	23.11	224	33.20	

[1] Data are from the National Health and Nutrition Examination Surveys. All data except for sample size are weighted accounting for the complex study design according to the directions of the National Center for Health Statistics. Data values are reported as *n*

(weighted percentage). Total of percentages may exceed 100 due to rounding. UIC, urinary iodine concentration; NHW, non-Hispanic white; NHB, non-Hispanic black; [2]*p* value obtained from the Wald chi-square test (**p*< 0.05, ***p* <0.01); [3] PIR, family poverty-income ratio (low: 0–1.85; medium: 1.85 < to 3.5; high: >3.5); [4] smoking status defined by a serum cotinine concentration (low: <0.015 mg/L; medium: 0.015 to <10 mg/L; high: ≥10mg/L); [5]BMI: Underweight: <18.5 kg/m^2; normal weight: 18.5 to >25 kg/m^2; overweight: 25 to <30 kg/m^2; and obese: ≥30 kg/m^2; [6] reported taking supplement containing iodine within the past 30 days; [7]Calculated as total MET (metabolic equivalent task minutes)-min/week from self-reported leisure-time physical activities.

Table 4.2. Median UIC (µg/L) of US adults aged 20years and over by demographic and lifestyle characteristics, NHANES 2011-2012[1]

		mUIC	
		µg/L	*(95% CI)*
	Overall	126.6	(111.9, 141.2)
Sex	Male	145.6	(124.1, 167.1)
	Female	111.2*	(96.4, 126.0)
Age	20-39years	120.1	(98.1, 142.1)
	40-59years	113.9*	(94.6, 133.3)
	≥ 60years	157.3	(133.8, 180.9)
Race	NHW	120.2	(98.9, 141.4)
	NHB	135.1	(109.8, 160.4)
	NHA	128.9	(114.0, 143.8)
	Hispanics[2]	136.1	(113.9, 158.2)
Education	< High School	136.4	(113.4, 159.5)
	High School	127.8	(96.6, 159.1)
	> High School	121.4	(103.3, 139.5)
PIR	Low	141.0	(125.9, 156.1)
	Medium	120.4	(97.7, 143.1)
	High	117.1*	(97.7, 136.6)
Smoking	Low	129.9	(106.7, 153.1)
(serum cotinine)	Medium	130.1	(108.1, 151.9)
	High	113.8	(90.9, 136.8)
	Underweight	118.6	(71.5, 165.6)
BMI	Normal	111.0*	(95.4, 126.6)
	Overweight	138.8	(115.5, 162.1)
	Obese	139.2	(115.3, 163.1)
Supplement Use[3]	Yes	148.4	(124.5, 172.3
	No	121.8*	(106.7, 136.9)
Alcohol Use	None	133.7	(101.0, 166.5)
	> 0 to 1 drink/day	121.3	(96.3, 146.3)

	>1 to 2 drink/day		101.0	(72.1, 129.9)
	> 2 drink/day		140.3	(121.1, 159.4)
Physical Activity[4]	No Activity		129.8	(107.7, 151.6)
	0 to < 500 MET-min/wk		119.5	(87.2, 151.8)
	500 to <1000 MET min/wk		119.1	(95.3, 142.8)
	≥1000 MET-min/wk		138.7	(113.3, 163.9)
Waist				
Circumference	Men	≤ 102 cm	146.6	(124.0, 169.2)
		>102 cm	143.6	(114.0, 173.2)
	Women	≤ 88 cm	104.1*	(87.3, 120.8)
		>88 cm	116.8	(97.9, 135.7)

[1] Data are from the National Health and Nutrition Examination Surveys; [2] Other race/multiracial origin included in Hispanics but not shown separately. Notes: 95% confidence interval (95% CI), median Urinary iodine concentration (mUIC), µg/L. *represent statistically significant difference ($P < 0.05$) within the respective row they appear in. NHW, non-Hispanic white; NHB, non-Hispanic black; PIR, family poverty-income ratio (low: 0–1.85; medium: 1.85 < to 3.5; high: >3.5); smoking status defined by a serum cotinine concentration (low: <0.015 mg/L; medium: 0.015 to <10 mg/L; high: ≥ 10mg/L); BMI: Underweight: <18.5 kg/m^2; normal weight: 18.5 to >25 kg/m^2; overweight: 25 to <30 kg/m^2; and obese: ≥30 kg/m^2; [3]reported taking supplement containing iodine within the past 30 days; [4] Calculated as total MET (metabolic equivalent task minutes)-min/week from self-reported leisure-time physical activities.

Table 4.3 Unadjusted insulin resistance biomarkers by covariates categories for US adults, NHANES 2011-2012[1]

		FBG	Insulin	Hb1Ac	HOMA-IR
		mmol/L	*μU/mL*	*%*	
Sex	Male	5.7 ± 0.07	13.5 ± 0.70	5.5 ± 0.03	3.5 ± 0.20
	Female	5.4 ± 0.07	12.0 ± 0.70	5.4 ± 0.03	2.9 ± 0.13
	r^2, %	<1	<1	<1	<1
Age	20-39years	5.4 ± 0.05*	12.7 ± 0.60	5.3 ± 0.03**	3.1 ± 0.16
	40-59years	5.6 ± 0.10	13.3 ± 1.02	5.5 ± 0.03	3.5 ± 0.31
	≥ 60years	5.7 ± 0.15	11.6 ± 1.15	5.7 ± 0.06	3.1 ± 0.30
	r^2, %	2.8	<1	7	<1
Race	NHW	5.5 ± 0.04	12.4 ± 0.68	5.4 ± 0.03	3.1 ± 0.17
	NHB	5.5 ± 0.08	15.4 ± 0.52**	5.6 ± 0.02**	3.9 ± 0.13**
	NHA	5.4 ± 0.09	12.2 ± 1.21	5.5 ± 0.06	3.0 ± 0.35
	Hispanics	5.6 ± 0.09	12.9 ± 1.39	5.5 ± 0.03	3.4 ± 0.39
	r^2, %	<1	<1	1.3	<1
Education	< High School	5.8 ± 0.11**	13.9 ± 1.20	5.6 ± 0.03**	3.7 ± 0.30
	High School	5.5 ± 0.06	13.6 ± 0.90	5.4 ± 0.03	3.4 ± 0.25
	> High School	5.4 ± 0.04	12.2 ± 0.60	5.4 ± 0.03	3.0 ± 0.15
	r^2, %	1.5	<1	2.5	1
PIR	Low	5.5 ± 0.07	14.4 ± 0.79*	5.5 ± 0.03*	3.6 ± 0.24*
	Medium	5.6 ± 0.06	12.3 ± 0.88	5.4 ± 0.04	3.2 ± 0.27
	High	5.5 ± 0.08	10.9 ± 0.87	5.4 ± 0.04	2.7 ± 0.21

	r^2, %	<1	2.5	<1	2
Smoking	Low	5.5 ± 0.07	11.5 ± 0.73	5.4 ± 0.03	2.9 ± 0.17
(serum cotinine)	Medium	5.6 ± 0.09	12.9 ± 0.91	5.5 ± 0.03	3.3 ± 0.25
	High	5.6 ± 0.05	13.9 ± 0.77*	5.5 ± 0.02*	3.5 ± 0.18*
	r^2, %	<1	<1	<1	<1
BMI	Underweight	5.3 ± 0.11	16.7 ± 5.16	5.3 ± 0.05	4.1 ± 1.32
	Normal	5.3 ± 0.08	8.3 ± 0.68	5.3 ± 0.04	2.0 ± 0.16
	Overweight	5.5 ± 0.06	11.3 ± 0.80	5.4 ± 0.03	2.8 ± 0.19
	Obese	5.7 ± 0.07**	18.3 ± 1.00**	5.6 ± 0.04**	4.8 ± 0.27**
	r^2, %	3.1	18	3.8	18.2
Supplement Use[2]	Yes	5.5 ± 0.07	12.7 ± 1.53	5.4 ± 0.03	3.2 ± 0.43
	No	5.6 ± 0.04	12.8 ± 0.53	5.4 ± 0.03	3.2 ± 0.13
	r^2, %	<1	<1	<1	<1
Alcohol Use	None	5.4 ± 0.06*	13.1 ± 1.01	5.5 ± 0.03	3.3 ± 0.26
	> 0 to 1 drink/day	5.5 ± 0.15	10.5 ± 0.82**	5.5 ± 0.06	2.6 ± 0.22**
	>1 to 2 drink/day	5.7 ± 0.11	13.2 ± 1.44	5.3 ± 0.04	3.5 ± 0.42
	≥ 2 drink/day	5.6 ± 0.06	13.7 ± 0.59	5.4 ± 0.03	3.5 ± 0.14
	r^2, %	1.3	1.4	1.1	1.5
Physical Activity[3]	No activity	5.5 ± 0.03	14.3 ± 0.58	5.5 ± 0.03	3.6 ± 0.10
	0 to <500 MET-min/week	5.6 ± 0.13	12.5 ± 1.02	5.4 ± 0.05	3.2 ± 0.30
	500 to <1000 MET-min/week	5.5 ± 0.08	11.0 ± 0.83	5.4 ± 0.05	2.8 ± 0.20
	≥1000 MET-min/week	5.4 ± 0.09	9.6 ± 1.22**	5.3 ± 0.04**	2.4 ± 0.30**

	r^2, %	< 1	3.3	4.7	2.9
Waist Circumference	Male ≤ 102cm	5.6 ± 0.07	10.3 ± 0.70	5.4 ± 0.02	2.6 ± 0.18
	> 102cm	5.8 ± 0.08**	18.3 ± 1.30**	5.6 ± 0.04**	4.9 ± 0.39**
	r^2, %	1.1	14.8	4.4	14.2
	Female ≤88cm	5.1 ± 0.05	9.1 ± 1.21	5.3 ± 0.03	2.1 ± 0.28
	>88cm	5.6 ± 0.12**	14.0 ± 0.61**	5.5 ± 0.04**	3.5 ± 0.12**
	r^2, %	6	6.9	5	8.7

[1] Data are from the National Health and Nutrition Examination Surveys. NHW, non-Hispanic white; NHB, non-Hispanic black; PIR, family poverty-income ratio (low: 0–1.85; medium: 1.85 < to 3.5; high: >3.5); * represent Least significant differences (LSD) obtained from bivariate analysis in a linear regression test (*P <0.05, **P< 0.01); smoking status defined by a serum cotinine concentration (low: <0.015 mg/L; medium: 0.015 to <10 mg/L; high: ≥10 mg/L); BMI: Underweight: <18.5 kg/m^2; normal weight: 18.5 to >25 kg/m^2; overweight: 25 to <30 kg/m^2; and obese: ≥30 kg/m^2; [2] reported taking supplement containing iodine within the past 30 days; [3] Calculated as total MET (metabolic equivalent task minutes)-min/week from self-reported leisure-time physical activities.

Table 4.4 Insulin resistance profile by urinary iodine concentrations in US adults (by Sex), NHANES 2011 – 2012[1]

IR Measure	Sex	Low UIC (<100µg/L)	Normal UIC (≥100µg/L)	*P*[2]
FBG (mmol/L)	Male	5.8 ± 1.34	5.6 ± 0.06	0.0712
	Female	5.4 ± 0.08	5.5 ± 0.11	0.3580
Insulin (µU/mL)	Male	13.1 ± 1.44	13.7 ± 0.93	0.7719
	Female	12.0 ± 1.18	11.9 ± 1.00	0.9659
HbA1c (%)	Male	5.5 ± 0.06	5.5 ± 0.03	0.8086
	Female	5.4 ± 0.04	5.5 ± 0.04	0.0712
HOMA-IR	Male	3.5 ± 0.42	3.5 ± 0.27	0.9987
	Female	2.9 ± 0.30	2.9 ± 0.22	0.9901

[1] Data are from the National Health and Nutrition Examination Surveys. [2]*P* obtained from bivariate analysis ($P < 0.05$); Bivariate analysis was performed to estimate IR profile for subjects with Low UIC (< 100µg/L) and Normal UIC (≥ 100µg/L) by sex from NHANES 2011–2012.

Table 4.5 Insulin resistance profile by urinary iodine concentrations in US adults (by age group), NHANES 2011 – 2012[1]

IR Measure	age	Low UIC (<100µg/L)	Normal UIC (≥100µg/L)	*P*[2]
FBG (mmol/L)	20 – 39 y	5.3 ± 0.07	5.4 ± 0.07	0.5943
	40 – 59 y	5.7 ± 0.12	5.6 ± 0.12	0.3737
	≥ 60 y	5.9 ± 0.19	5.7 ± 0.19	0.6069
Insulin (µU/mL)	20 – 39 y	11.7 ± 0.88	13.4 ± 0.72	0.1720
	40 – 59 y	13.1 ± 0.94	13.5 ± 1.55	0.8295
	≥ 60 y	13.5 ± 3.31	11.2 ± 0.83	0.4694
HbA1c (%)	20 – 39 y	5.3 ± 0.03	5.3 ± 0.04	0.1217
	40 – 59 y	5.5 ± 0.05	5.5 ± 0.04	0.4999
	≥ 60 y	5.8 ± 0.07	5.7 ± 0.07	0.0720
HOMA-IR	20 – 39 y	2.9 ± 0.23	3.3 ± 0.19	0.2103
	40 – 59 y	3.5 ± 0.30	3.5 ± 0.45	0.9894
	≥ 60 y	3.6 ± 0.85	2.9 ± 0.25	0.4394

[1] Data are from the National Health and Nutrition Examination Surveys. [2]*P* obtained from bivariate analysis ($P < 0.05$); Bivariate analysis was performed to estimate IR profile for subjects with Low UIC (< 100µg/L) and Normal UIC (≥ 100µg/L) by age groups from NHANES 2011–2012.

Table 4.6 Prevalence of insulin resistance in relation to urinary iodine concentration in US adults, NHANES 2011-2012[1]

IR Measure	Model	Low UIC (<100µg/L)	Normal UIC (≥100µg/L)	*P*[2]
		AOR (95% CI)	**Referent**	
Elevated FBG (≥ 5.6mmol/L)	1	1.08 (0.72 - 1.62)	1	0.7036
	2	1.11 (0.77 -1.59)	1	0.5630
Elevated Insulin (> 9 µU/ml)	1	0.99 (0.60 -1.65)	1	0.1877
	2	0.99 (0.59 - 1.67)	1	0.9926
HbA1c (≥ 5.7%)	1	0.83 (0.57 - 1.21)	1	0.3091
	2	0.91 (0.64 - 1.28)	1	0.5502
HOMA-IR (≥ 2.6)	1	0.86 (0.55 - 1.34)	1	0.4744
	2	0.83 (0.56 - 1.25)	1	0.3489

[1] Data are from the National Health and Nutrition Examination Surveys. Multiple logistic regression was performed to estimate odds ratio for insulin resistance for subjects from the NHANES 2011–2012 in two models: unadjusted (model 1) and adjusted for sex, age, race/ethnicity, education, income, iodine-supplement use, smoking, alcohol consumption, BMI, waist circumference, physical activity (model 2). UIC, urinary iodine concentration; AOR, adjusted odds ratio; 95% CI, 95% confidence interval. [2]*P* obtained from multiple logistic regression model with diagnosis of insulin resistance as the outcome variables (**P*< 0.05, ***P*<0.01).

Table 4.7 Prevalence of insulin resistance in relation to urinary iodine concentration in US male adults, NHANES 2011-2012[1]

IR Measure	Model	Low UIC (<100µg/L)	Normal UIC (≥100µg/L)	*P*[2]
		AOR (95% CI)	**Referent**	
Elevated FBG (≥5.6mmol/L)	1	0.92 (0.57 - 1.50)	1	0.7302
	2	0.87 (0.52 -1.45)	1	0.5682
Elevated Insulin (>9 µU/ml)	1	1.00 (0.51 -1.97)	1	0.1877
	2	1.00 (0.50 - 2.01)	1	0.9903
HbA1c (≥5.7%)	1	1.26 (0.74 - 2.16)	1	0.3705
	2	1.48 (0.92 - 2.39)	1	0.0993
HOMA-IR (≥2.6)	1	0.88 (0.43 - 1.79)	1	0.6991
	2	1.23 (0.69 - 2.17)	1	0.4484

[1] Data are from the National Health and Nutrition Examination Surveys. Multiple logistic regression analysis was performed to estimate odds ratio for insulin resistance in male adults from NHANES 2011–2012 in two models: unadjusted (model 1) and adjusted for age, race/ethnicity, education, income, iodine-supplement use, smoking, alcohol consumption, BMI, waist circumference, physical activity (model 2). UIC, urinary iodine concentration; AOR, adjusted odds ratio; 95% CI, 95% confidence interval. [2]*P* value obtained from multiple logistic regression model with diagnosis of insulin resistance as the outcome variables (**P* <0.05, ***P*<0.01).

Table 4.8 Prevalence of insulin resistance in relation to urinary iodine concentration in US female adults, NHANES 2011-2012[1]

IR Measure	Model	Low UIC (<100µg/L)	Normal UIC (≥100µg/L)	*P*[2]
		AOR (95% CI)	**Referent**	
Elevated FBG (≥5.6mmol/L)	1	1.52 (0.94 - 2.44)	1	0.0839
	2	1.73 (1.09 - 2.72)	1	0.0211*
Elevated Insulin (>9 µU/ml)	1	1.04 (0.58 -1.87)	1	0.8873
	2	1.08 (0.54 - 2.16)	1	0.8120
HbA1c (≥5.7%)	1	0.56 (0.34 - 0.90)	1	0.0208*
	2	0.58 (0.34 - 1.02)	1	0.0563
HOMA-IR (≥2.6)	1	0.91 (0.46 - 1.80)	1	0.7734
	2	0.56 (0.32 - 0.99)	1	0.0478*

[1]Data are from the National Health and Nutrition Examination Surveys. Multiple logistic regression analysis was performed to estimate odds ratio for insulin resistance in female adults from NHANES 2011–2012 in two models: unadjusted (model 1) and adjusted for age, race/ethnicity, education, income, iodine-supplement use, smoking, alcohol consumption, BMI, waist circumference, physical activity (model 2). UIC, urinary iodine concentration; AOR, adjusted odds ratio; 95% CI, 95% confidence interval. [2]*P* value obtained from multiple logistic regression model with diagnosis of insulin resistance as the outcome variables (*$P < 0.05$, ** $P < 0.01$).

CHAPTER 5

DISCUSSION

The objectives of the present study were to 1) identify socioeconomic and lifestyle variables affecting markers of UIC and IR (fasting glucose, insulin, HbA1c, and HOMA-IR); 2) determine the association of UIC with markers of IR; and to 3) estimate the risks of IR by UIC in adults using NHANES 2011-2012. This analysis shows that the median UIC of adults in the U.S population is above the minimum cut-off for normal iodine status, although there are a few vulnerable groups. Those with significantly lower mUIC were more likely to be female, young, high income level, and not taking iodine-containing supplements. Our results identifying several socioeconomic and lifestyle factors associated with IR are consistent with the scientific literature (i.e., age, race, education, income, smoking, BMI, alcohol use, waist circumference, and physical activity) (Meigs, 2003; Spanakis and Golden, 2013; Moore et al., 2014; Kim et al., 2017). There were no significant associations, unadjusted or adjusted for socioeconomic and lifestyle factors, between measures of IR and UIC for adults in general, and likewise, for males. This was not the case in females, however, as some of the IR results were significant but conflicting. Females with normal UIC had greater risks for elevated HbA1C and HOMA-IR, while those with low UIC had a greater risk for high FBG. This inconsistency may in part be explained by differences in the diagnostic limitations of each measurement (i.e., HbA1C is a long-term and FBG is a short-term indicator of IR) and/ or the confounding effects of other better-recognized IR predictors, especially income and body weight status. Therefore, taken together, our results only partially support our hypothesis that UIC is associated with the odds of IR in the US population.

The finding of an increased risk of elevated FBG, a marker of prediabetes, in female adults with low iodine status is noteworthy and worthy of further exploration.

5.1 Most US Adults Have Adequate Iodine Status, although Vulnerable Groups Exist

UIC is a good marker of the recent dietary intake of iodine. In this analysis of NHANES 2011-2012, we found that even though adults aged 20 years and older in the U.S population had a mUIC of 126.6µg/L [indicative of iodine sufficiency using WHO criteria (WHO, 2013)], iodine status appears to be declining over the past decade. Analyses of NHANES reported a mUIC of 144µg/L for the 2009-2010 cycle and 164µg/L for the 2007-2008 cycle (Caldwell et al., 2013). As in previous NHANES survey periods, women had significantly lower UIC than men (Caldwell et al., 2008). Similar to our findings, Pan et al., 2013 reported that more than 30% of women studied had UIC below the target of 100µg/L. Likewise, Stagnaro-Green et al., 2015 revealed that one out of every nine women (11%) with low UIC had thyroid function test consistent with SCH especially in women of reproductive age (WRA). Thus, it is possible that without changes in dietary intake, some women may have insufficient intake especially WRA.

Across age groups in the general population, 40-59 years group had the lowest UIC (113.9µg/L) which was shown last year by Herrick et al., 2018. It has been speculated that within the higher spectrum of this age group where menopause occurs, there is an interaction between body iodine status and menopausal period, although, the mechanism of action is unknown (Korkmaz et al., 2015).

By race, non-Hispanic Asians had lower mUIC compared to NHB and Hispanic groups. This could be explained by similar results reported by Herrick et al., 2018 in which high soy

consumption among non-Hispanic Asians was associated with low mUIC. Compared to cow's milk, soymilk does not contain high amounts of iodine (Borucki Castro et al., 2010). Soymilk and soy products also contain goitrogens that block the uptake of iodine by the thyroid; thus, having low iodine intake reflected by low mUIC may render these individuals susceptible to hypothyroidism (Doerge and Sheehan, 2002; Teas et al., 2007).

Individuals with high income had the lowest iodine status, with mUIC slightly above the "normal" cut-off (117.1µg/L). According to Zou et al., 2015, PIR and occupation are influencing factors for having a lower UIC. Causes have been attributed to individual attitudinal and behavioral responses to consumption of iodine-rich foods especially iodized salt. People with higher incomes prefer non-iodized salt despite the higher cost and can also be prone to "fast foods" eating habits which are largely cooked with non-iodized salt (Zou et al., 2014).

Given the role of iodine in thyroid hormone production, it is tempting to forecast that those with higher BMIs would have lower iodine status based on the ample evidence for compromised thyroid hormone status in the obese (Knudsen et al., 2005; Fox et al., 2008). However, individuals in our study who were overweight or obese had higher iodine status compared to normal BMI. This is most likely due to excess energy intake, the most common direct cause of overweight/obesity, contributing to incidentally greater intakes of iodine simply because of greater amounts of total food eaten. In support of this, Vega-Vega et al., 2018 recently showed that within a Mexican cohort (a country which also has a national salt iodization program), obese subjects had higher sodium intakes than overweight and normal BMI individuals. Furthermore, although adequate iodine availability is essential to the production of thyroid hormone, most of the plausible biological explanations for the relationship between low

thyroid hormone status and obesity are related to adipose-derived factors that have direct detrimental effects on the thyroid (Fox et al., 2008).

5.2 Socioeconomic and lifestyle factors associated with IR are consistent with the scientific literature

Metabolic syndrome (MetS), a cluster of metabolic abnormalities linked to IR is associated with an increased risk of type 2 diabetes mellitus (T2D). In our present study, we saw a positive correlation in IR biomarkers across age with the exception of fasting insulin which was decreased in those ≥60 years of age. Muller et al., 1996 noted that insulin secretion seems to decrease with age even after adjustments for differences in adiposity, fat distribution and physical activity. This may be the reason for glucose intolerance in the older population even after improvements have been made in their lifestyle. In-line with our findings on the link between education and IR, others have demonstrated that low education increases the odds of MetS (Moore et al., 2014). Food consumption pattern consisting of lower intakes of fruit, and milk; higher intakes of soft drink are common mediators for this prevalence (Kim et al., 2017).

Not surprisingly, our analysis revealed that greater BMI and waist circumference significantly impacted IR. This is supported by numerous studies showing that higher BMI and greater waist circumference are associated with poor glucose homeostasis (Meigs, 2003; Gobato et al., 2014; Jung et al., 2018). A study by Auchincloss et al., 2007 reported a 13% increase in HOMA-IR for every 1.7kg/m^2 increase in BMI thus, increasing the risk for MetS and progression into chronic diseases. Relatedly, our study revealed a significant negative correlation between physical activity and IR, an observation also well-documented (Fujita et al., 2019). Like the other

statistically-significant socioeconomic/lifestyle factors included in this examination of NHANES data, the scientific literature is replete with research that likewise shows relationships between IR and race (Spanakis and Golden, 2013), alcohol use (Tatsumi et al., 2018) and smoking (Haj et al., 2016; Yashima et al., 2000).

5.3 Significant Association between FBG and UIC in Adult Females

The role of macronutrient intake on IR in humans have been well-studied (Minich and Bland, 2008; Basem et al., 2018). However, the effects of micronutrients consumption on the underlying mechanisms of IR– especially between sex and age groups– has yet to be thoroughly investigated. In this analysis, UIC<100µg/L in adult females is associated with a greater risk for abnormalities in blood glucose levels compared to adult males. This finding is consistent with previous research regarding IR related to iodine status. Investigations by Chubb et al., 2005 and Song et al., 2017 revealed that females with thyroid dysfunction have greater risk for T2D over males although no mechanism of action was examined. Similar animal studies have shown the role of iodine via TH on glucose uptake in skeletal muscle, liver and adipose tissues (Potenza et al., 2009; Weinstein et al., 1994). The possible mechanism of action is the increase of glucose uptake via GLUT4 in skeletal muscle which has been shown in hypothyroid rats treated with T3 (Teixeira et al., 2012).

Furthermore, reports on the growing cluster of metabolically obese, normal-weight (MONW) individuals in the world (Ruderman et al., 1998; Dvorak et al., 1999; Chen et al., 2014; Furukawa and Kobayashi, 2019) could explain our findings that women with normal BMI and low UIC are more susceptible to glucose abnormalities. For example, one study of 465 healthy

volunteers (251 were women), designed to describe the prevalence of IR among normal weight, overweight, and obese individuals, found that 16% in the most IR tertile were of normal weight (BMI < 25.0 kg/m2) (Mclaughlin et al., 2014). Additionally, there are studies to suggest that different populations may be at greater risk for prediabetes and T2D in the absence of overweight and obesity (Maskarinec et al., 2009; Misra, 2018). For example, a study using data from NHANES and CARRS reported that Asian-Indians had 4.6 times greater prevalence of diabetes in the normal weight category than white individuals (Gujral et al., 2018). This calls for further exploration on possible crosslinks between iodine status, IR and BMI in Asian population who are majorly within normal BMI and found to have suboptimal mUIC compared to other ethnicities (Herrick et al., 2018). Therefore, considering iodine's role via thyroid hormone in thermogenesis and metabolism, it may be speculated that iodine insufficiency-induced SCH could be a contributor predisposing one to metabolic abnormalities like prediabetes. Thus, including an assessment of iodine status in the treatment plan of those normal-body weight patients presenting with symptoms of prediabetes, especially women, seems prudent.

Despite public measures like salt iodization, iodine status remains suboptimal in a large proportion of women (Johner et al., 2011; Zimmermann and Andersson, 2012). In support of these observations, our analysis demonstrates that women are more likely to have low UIC than men. Possible contributors to this include limited availability of iodine-containing supplements in the marketplace and poor adherence. Unlike vitamin D (another nutrient deficiency historically considered to be a public health problem), many multi-vitamin/mineral preparations do not contain iodine. In our study, only a small proportion (~ 18%) of the U.S population was found to be taking iodine-containing supplements; and those who consumed one had

significantly higher mUIC compared with individuals who did not. This is supported by other studies such as Gregory et al., 2009. Moreover, use of iodine supplementation has been shown to lead to higher UIC, supporting the efficacy of supplements when taken regularly (Brucker-Davis et al., 2013; Glinoer et al., 1995; Blumenthal et al., 2012).

Another possible contributing factor to the poorer iodine status of women is the limited knowledge of the health consequences of iodine deficiency among healthcare providers (Burns et al., 2018). A study by Leo et al., 2017 revealed that within 199 midwives and 277 obstetricians studied, 75% of U.S obstetricians and midwives do not recommend an adequate amount of iodine during preconception. This could fuel an increase in SCH among women as well as iodine deficiency associated consequences.

Notwithstanding, our present study also shows unexpected decreased risks for elevated HOMA-IR and HbA1c in female adults with UIC<100μg/L. These observations could be explained by the presence of shared but conflicting environmental and lifestyle factors associated with iodine status and IR. As an example, excess body fat gain, particularly in the deep abdominal area, is known to be associated with an increase in insulinemia and glucose intolerance (Trembley, 1995). In our study, the majority of female respondents with BMI ≥ 25kg/m^2 and waist circumference >88 cm not only had higher levels of each of the IR measurements, but they also had higher iodine status. As previously stated, this is most likely related to greater food/energy intake and thus more possible iodine opportunities. This calls for further research using experimental designs that control for these confounders. Furthermore, the differences in the results between the UIC groups maybe due to the diagnostic limitation of HbA1c, a long-term reflection of average blood glucose over the past 2 to 3-months (Meigs,

2003) compared to FBG which is a short-term reflection of previous day's carbohydrate intake and insulin response.

5.4 Strengths, Limitations, and Future Research

This study has several strengths and limitations. First, NHANES is a nationally representative, standardized survey on a multitude of health-related issues. This ensure that results are generalizable and have a high level of validity. The randomization technique in NHANES used in selection of individual across the United States minimizes selection bias. In addition, the use of trained personnel ensures a standardized survey.

A study limitation is the well-known variability in UIC. UIC are highly variable and represent the recent dietary intake of iodine rather than the usual intake. Due to this variation, a sample of 100 spot urine test samples is needed to produce the estimates of UIC with a precision range of ~10 %, and a sample of 500 is needed for a precision range of ~5 % (Zou et al., 2015; Andersen et al., 2008). In addition, assessing iodine status based on UIC could not determine the actual amount of iodine intake from dietary sources. To overcome recognized limitations, we used the grouping approach. Although we had significant findings regarding the association between UIC and IR with this approach, association should be interpreted with circumspection. More so, Understanding the impact of actual dietary iodine intakes and individual's iodine status on IR biomarkers is worth further investigation. Due to variation in individual intake, neither a single 24-hr recall nor a single spot urine sample captures a consistent individual iodine status as measured by UIC. We therefore employ that caution should be exercised when interpreting values from linear regression analysis between UIC and insulin resistance biomarkers on an

individual basis. Lastly, in this present study we highlighted that those with low UIC especially female adults had increased risk of glucose abnormalities though our findings are based on cross-sectional survey data. This makes it difficult to determine a causal relationship between UIC and IR.

The present research based on a cross-sectional study makes it difficult to determine a causal relationship between UIC and IR. It is recommended that further researches like randomized feeding trials be carried out to ascertain the direct impact of dietary iodine intakes on IR biomarkers in animal and human studies especially the adult female population who are more vulnerable to iodine deficiency as seen from our study and previous literatures. Particularly, normal BMI should be studied to understand the casual effect of iodine intake on IR profiles without the presence of confounding factors like overweight and obesity.

CONCLUSION

In conclusion, although the median UIC of adults in the U.S population falls within the range of optimal iodine status, continuous close monitoring of groups like women and across age groups vulnerable to low mUIC are warranted as there appears to be a decline in iodine status in the general population over the past decade. Of most concern in this study is the possible increase risk for pre-diabetes in women with low UIC<100µg/L as evidenced by greater FBG, especially among those in middle age with normal BMI. However, more research is needed to confirm a causal relationship between iodine status and IR.

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APPENDIX

Controlled covariates in adjusted model for IR biomarkers in UIC levels of Female Adults in the US Population, NHANES 2011-2012[1].

IR Measure	Covariates	groups	AOR (95% CI)	Referent	*P*[2]
Elevated FBG (≥ 5.6mmol/L)	**Age**	40 – 59 y	1.92 (0.89 – 4.11)	20 – 39 y	0.6912
		≥ 60 y	2.91 (1.33 – 6.36)	20 – 39 y	0.0221*
	Smoking (Serum Cotinine)	Medium	1.39 (0.59 – 3.23)	Low	0.5904
		High	2.81 (0.95 – 8.28)	Low	0.0668
	BMI	Underweight	0.88 (0.12 – 6.16)	Normal	0.5439
		Overweight	0.21 (0.05 – 0.88)	Normal	0.0249*
		Obesity	0.50 (0.12 – 2.11)	Normal	0.8359
	Waist Circumference	> 88 cm	7.22 (1.16 – 45.0)	≤ 88 cm	0.0360*
Elevated Insulin (> 9 µU/ml)	**Race**	NHW	1.09 (0.56 - 2.12)	NHA	0.9694
		NHB	1.35 (0.72 - 2.55)	NHA	0.1466
		Hispanics	0.97 (0.58 - 1.64)	NHA	0.3592
	Smoking (Serum Cotinine)	Medium	1.54 (0.86 - 2.76)	Low	0.5518
		High	1.72 (1.02 - 2.90)	Low	0.1965
	BMI	Underweight	1.29 (0.35 - 4.82)	Normal	0.5565
		Overweight	0.56 (0.12 - 2.64)	Normal	0.3933

		Obesity	0.83 (0.28 - 2.45)	Normal	0.8530
	Waist Circumference	> 88 cm	3.74 (1.00 - 13.9)	≤ 88 cm	0.0496*
HbA1c (≥ 5.7%)	**Age**	40 – 59 y	2.13 (1.32 - 3.43)	20 – 39 y	0.8085
		≥ 60 y	5.26 (2.16 - 12.8)	20 – 39 y	0.0091**
	Education	< High School	0.97 (0.52 - 1.79)	> High School	0.8878
		High School	0.88 (0.42 - 1.83)	> High School	0.6939
	BMI	Underweight	0.14 (0.02 - 1.04)	Normal	0.0322*
		Overweight	0.87 (0.44 - 1.71)	Normal	0.5915
		Obesity	2.23 (0.96 - 5.18)	Normal	0.0007**
	Waist Circumference	> 88 cm	1.56 (1.08 - 2.25)	≤ 88 cm	0.0205*
	Physical Activity[3]	No Activity	2.64 (0.77 - 9.01)	≥1000 MET-min/wk	0.0994
		0 to < 500 MET-min/wk	1.67 (0.59 - 4.84)	≥1000 MET-min/wk	0.9787
		500 to <1000 MET min/wk	1.83 (0.38 - 8.74)	≥1000 MET-min/wk	0.8453
HOMA-IR (≥ 2.6)	**BMI**	Underweight	0.25 (0.05 - 1.16)	Normal	0.0677
		Overweight	0.71 (0.31 - 1.61)	Normal	0.8987
		Obesity	1.68 (0.78 - 3.64)	Normal	0.0010**
	Smoking (Serum Cotinine)	Medium	1.45 (0.81 - 2.58)	Low	0.7650
		High	1.79 (0.82 - 3.90)	Low	0.2404
	Alcohol Use	None	0.97 (0.45 - 2.09)	> 0 to 1 drink/day	0.0406*
		>1 to 2 drink/day	0.37 (0.15 - 0.95)	> 0 to 1 drink/day	0.0549
		> 2 drink/day	0.37 (0.12 - 1.12)	> 0 to 1 drink/day	0.1035

Waist Circumference	> 88 cm	2.32 (1.47 - 3.67)	≤ 88 cm	0.0012**
Supplement Use[4]	No	1.07 (0.51 - 2.25)	Yes	0.8537

Note: The covariates above were statistically significant in bivariate logistic regression for each IR profile and thus, used in the adjusted model analysis with a sub-group from each covariate made a referent. [1] Data are from the National Health and Nutrition Examination Surveys. [2]*P*-value obtained from adjusted logistic regression model with diagnosis of abnormal IR biomarkers as the outcome variables (* $P < 0.05$, ** $P < 0.01$). NHW, non-Hispanic white; NHB, non-Hispanic black; Smoking status defined by a serum cotinine concentration (low: <0.015 mg/L; medium: 0.015 to <10 mg/L; high: ≥10 mg/L); BMI: Underweight: <18.5 kg/m^2; normal weight: 18.5 to >25 kg/m^2; overweight: 25 to <30 kg/m^2; and obese: ≥30 kg/m^2; [3]Calculated as total MET (metabolic equivalent task minutes)-min/week from self-reported leisure-time physical activities; [4]Reported taking supplement containing iodine within the past 30 days.