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Is low iodine a risk factor for cardiovascular disease in Americans without thyroid dysfunction? Findings from NHANES

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Abstract *Background and aims:* Low body iodine levels are associated with cardiovascular disease, in part through alterations in thyroid function. While this association suggested from animal studies, it lacks supportive evidence in humans. This study examined the association between urine iodine levels and presence of coronary artery disease (CAD) and stroke in adults without thyroid dysfunction.
Methods and results: This cross-sectional study included 2440 adults (representing a weighted n = 91,713,183) aged ≥40 years without thyroid dysfunction in the nationally-representative 2007–2012 National Health and Nutrition Examination Survey. The age and sex-adjusted urine iodine/creatinine ratio (aICR) was categorized into low (aICR<116 μg/day), medium (116 μg/day ≤ aICR < 370μg/day), and high (aICR ≥ 370μg/day) based on lowest/highest quintiles. Stroke and CAD were from self-reported physician diagnoses. We examined the association between low urine aICR and CAD or stroke using multivariable logistic regression modeling. The mean age of this population was 56.0 years, 47% were women, and three quarters were non-Hispanic whites. Compared with high urine iodine levels, multivariable adjusted odds ratios aOR (95% confidence intervals) for CAD were statistically significant for low, aOR = 1.97 (1.08–3.59), but not medium, aOR = 1.26 (0.75–2.13) urine iodine levels. There was no association between stroke and low, aOR = 1.12 (0.52–2.44) or medium, aOR = 1.48 (0.88–2.48) urine iodine levels.
Conclusion: The association between low urine iodine levels and CAD should be confirmed in a prospective study with serial measures of urine iodine. If low iodine levels precede CAD, then this potential and modifiable new CAD risk factor might have therapeutic implications.

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Introduction

Thyroid hormones, important regulators of metabolism, require iodine for their structure and function [1]. While it is estimated that two-thirds of iodine is in the thyroid gland, extra thyroidal organs – including the heart, kidney, and liver – also contain iodine [2]. Despite the acknowledged importance of iodine to the growth, maturation, and functioning of humans, its role on the cardiovascular system has not been well-studied. Previous studies have focused on the indirect effects of iodine on the cardiovascular system via its alteration of thyroid function [3]. For example, iodine deficiency can cause hypothyroidism and both overt and subclinical hypothyroidism have been shown to be associated with hyperlipidemia and coronary artery disease [1]. Iodine treatment in hypothyroid patients with iodine deficiency has also been shown to reduce serum lipid levels [4]. However, the direct effects of iodine on cardiovascular disease (CVD), independent of thyroid function, remain unknown.

Evidence suggesting an independent association between low iodine levels and CVD presently exists. Low iodine levels have been associated with several risk factors for CVD, including hyperlipidemia and insulin resistance, in both animal and human studies [5–9]. However, prior studies in humans included participants with thyroid dysfunction, and could not disentangle the direct effects of iodine from that of thyroid dysfunction. Also, no study has examined the relation of low urine iodine levels with the presence of CVD.

Using data from the National Health and Nutrition Examination Survey (NHANES), we examined the hypothesis that low iodine levels are associated with an increased prevalence of CVD, namely coronary artery disease (CAD) and stroke, in adults without thyroid dysfunction.

Methods

Study design and sample

In this cross-sectional study, we used three cycles of data from NHANES 2007–2012. NHANES selects nationally representative samples of the United States civilian non-institutionalized population on a biennial basis using stratified multistage probability sampling. The National Center for Health Statistics Ethics Review Board has approved the NHANES study protocol, and all participants provided written informed consent. The University of Massachusetts Medical School Internal Review Board did not require an approval for this study because the NHANES data were publicly available and de-identified.

Study population

We identified adults aged ≥40 years whose urine samples were tested for iodine (n = 3797). We excluded 329 adults with a self-reported history of thyroid disease, 12 adults who were currently taking thyroid hormones or antithyroid medications, and 584 adults who currently had thyroid dysfunction, defined by a TSH level <0.5 mU/L or >5.0 mU/L, free thyroxine <0.6 ng/dL or >1.6 ng/dL, and free triiodothyronine <2.5 pg/mL or >3.9 pg/mL [10]. Since iodine metabolism may differ in pregnant women and patients with kidney disease, we excluded three pregnant women and 99 participants with a self-reported history of chronic kidney disease/failure. We excluded 12 participants who reported that the age of their first CVD diagnosis was younger than 30 years old since these may be the results of hereditary or drug-related disease as well as 134 adults with missing data on dietary recall and 99 adults with missing data on other key variables. The final study sample included 2440 adult men and women aged 40 years or older (weighted n = 91,713,183).

Operational definition of urinary iodine

Urine was sampled from all adults in the 2007–2008 wave and in a one third random sample of participants in the 2009–2012 survey waves. Study coordinators collected, stored, and shipped the specimens to the central laboratory following standardized procedures [11]. Urine iodine levels were determined using the Inductively Coupled Plasma Dynamic Reaction Cell Mass spectroscopy method [11]. Abnormal urine iodine results (<50 μg/L or >800 μg/L) were retested with a new sample preparation. Urine iodine results that were higher than the reliable range were retested by an extra dilution method and compared with standard external materials. Any abnormal values were only confirmed and reported if the comparison results were within 10% of the original results [11].

We used the adjusted urine iodine/creatinine ratio (aICR), which was calculated by [spot urine iodine (μg/dl)/spot urine creatinine (mg/dl)] × predicted 24 h urine creatinine excretion (mg/day), to approximate the 24 h urine iodine level [12]. Since almost all body iodine excretion is in the urine, urine iodine levels can represent total body iodine levels [2]. While a single measurement of urine iodine can vary due to time associated variation of urine volume, adjustment for creatinine excretion, and further for age and sex, would offset time-related variation in urine iodine levels and increases the reliability of the urine iodine measurement [12]. The age and sex-adjusted urine iodine/creatinine ratio has been shown to be highly correlated with 24 h urine iodine excretion (r = 0.77) [13]. Details about this method are described elsewhere [12]. Because there are no established cut points of aICR to denote low iodine levels, and because there was no distinct point that separated the distribution of aICR among persons with and without CVD in our dataset, we defined urine iodine/creatinine ratio as low (aICR < 116 μg/day), medium (116 μg/day to less than 370 μg/day), and high (aICR ≥ 370 μg/day) using the lowest and highest quintiles of their distribution in this population as cutoffs.

Cardiovascular disease

We used a self-reported physician diagnosis of coronary artery disease (CAD) and stroke as assessed by the question