Title
SELENIUM AND BMI: A DISSERTATION STUDY

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Selenium and BMI: A Dissertation Study

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Selenium and BMI: A Dissertation Study

Karina Demikhova

Abstract

Obesity, defined by BMI, is an escalating health concern. Selenium is an essential trace mineral involved in many metabolic activities, including the production of antioxidant enzymes, fat accumulation, and the conversion of inactive thyroid- T4 to the active form- T3, all of which impact BMI. However, little is known about the relationship between selenium and BMI. Furthermore, the impact of menopause, T3, and physical activity on this relationship has not been evaluated. This study aimed to 1) map the currently available evidence on the selenium level and BMI using Arksey and O'Malley's scoping review framework, 2) investigate the relationship between serum selenium, BMI, and the menopausal status in 2,130 women who participated in the National Health and Nutrition Examination Survey (NHANES 2011-2012), and 3) analyze mediating effects of T3 and physical activity in the selenium and BMI relationship in 1,341 NHANES (2011-2012) adult participants. This cross-sectional study applied descriptive statistics, t-test, multiple linear regression models, and multilevel structural equation modeling for analysis. The scoping review identified conflicting findings, ranging from an inverse association between selenium to BMI to the positive association of low selenium with overweight and obesity. Adjusted for demographic factors, no statistically significant relationship between selenium and BMI, menopause, T3, or physical activity was found in our analysis. Postmenopausal women in our study had a significantly higher prevalence of obesity than premenopausal women while consuming significantly fewer calories per day. Men in our study had lower BMI, higher selenium and T3 levels, higher daily caloric intake, and lower activity levels than women participants. Future studies need to 1) identify and evaluate other metabolically important factors as potential mediating variables, 2) employ a longitudinal study design to capture changes in selenium, T3, and PA over time, and 3) include populations with selenium deficiency and selenium-replete participants to capture a broader range of serum levels and their effects on BMI values.

Keywords: Selenium, BMI, Menopause, T3, Physical Activity, Adults

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CHAPTER ONE

Dissertation Outline

This dissertation aims to investigate the role of blood selenium levels in body weight and test the impact of menopausal status, triiodothyronine (T3), and physical activity (PA) levels on the relationship between selenium and Body Mass Index (BMI) in US adults. It is organized into five chapters. The first chapter introduces issues related to obesity, provides information on serum selenium, T3, and PA, and describes a theoretical model for selenium and BMI to structure this dissertation study. The second chapter provides a scoping review of the existing literature about the relationship between blood selenium levels, average PA level, and BMI in US adults. The third chapter evaluates the relationship between serum selenium and BMI and the moderating role of menopause among adult women in the US using data from the National Health and Nutrition Examination Survey (NHANES 2011-2012). The fourth chapter examines the mediating role of T3 and PA in the relationship between serum selenium levels and BMI among US adults using data from the NHANES (2011-2012). The last chapter synthesizes the results, proposes future research recommendations, and provides the conclusion for this dissertation research.

Introduction to the Problem

Decades after the realization of obesity as a significant public health concern, rates of overweight and obesity continue to rise dramatically across all demographics (WHO, 2020). BMI is a popular screening tool to define overweight and obesity. According to the Center for Disease Control (CDC), in 2017-2018, 73.6% of US adults were overweight, including obesity (CDC, 2021). Defined as BMI greater than 30, obesity levels have increased from 26% to nearly 43% since 2008 (CDC, 2021). The estimated annual medical cost of obesity for a non-institutionalized population of adults aged 18 and older in the US was $342.2 billion in 2013 (Biener, Cawley, & Meyerhoefer, 2017).

Overweight and obesity significantly increase the risk for medical morbidity and mortality (Olson et al., 2019), placing individuals at an increased risk for cancer, cardiovascular disease, high blood pressure, stroke, diabetes, obstructive sleep apnea, asthma, and high cholesterol, all of which are among the leading causes of death among adults in the US (CDC, 2021). The current obesity trends are especially concerning for women. While the prevalence of obesity is similar in women and men, 10% of adult women are considered to have extreme obesity (BMI > 40), double that of men (5.5 %) (NIH, 2017). Extreme obesity further elevates the risk of obesity-related complications, such as diabetes, coronary heart disease, and end-stage renal disease (Hsu et al., 2006; Li et al.t, 2006). Obesity prevalence varies dramatically between racial, ethnic, sex, and socioeconomic groups, including income and education (CDC, 2020). Therefore, demographic and socioeconomic factors could influence the outcomes of obesity-related research and should be included in the overall analysis.

Selenium, Menopause, T3, and PA

Selenium is an essential trace mineral element that modulates oxidative stress by regulating the production of selenoenzyme- glutathione peroxidase (Touat-Hamici et al., 2014). Selenium is involved in thyroid hormone metabolism, reproductive health, cancer, inflammation, cardiovascular function, osteoporosis, diabetes, inflammation, and DNA synthesis (Alehagen & Aaseth, 2015; Karalis, 2019; Lewandowska et al., 2019; Sun et al., 2013; Oliva et al., 2019; Touat-Hamici et al., 2014 Wang et al., 2019). Selenium also plays an essential role in adipocyte hypertrophy and abdominal fat accumulation (Kim et al., 2012). Selenium levels significantly decline with age (Letsiou et al., 2014).

While recent findings suggest that high dietary selenium intake is associated with a healthy weight (Wang et al., 2016), the evidence on the relationship between blood selenium level and BMI remains conflicting. A wide range of findings includes a significant inverse association between serum selenium and BMI (Zhong et al., 2018), no significant differences between obese and non-obese participants concerning selenium (Ghayour-Mobarhan et al., 2005), a significant reduction in serum selenium level among morbidly obese female patients seeking bariatric surgery (Alasfar et al., 2011), a significant quadratic relationship with BMI, being lower in individuals at the low and high ends of the BMI range (Combs et al., 2011), and the association of low serum selenium with overweight and obesity in premenopausal females (Kimmons et al., 2006). Therefore, an updated and comprehensive summary of the current state of the science related to the serum selenium level and BMI is warranted.

Metabolic changes in women during menopause are associated with increased BMI and visceral fat accumulation (Wang et al., 2019). Postmenopausal women experience higher total body fat mass and accumulation of adiposity than premenopausal women (Davis et al., 2012; Razmjou et al., 2018). Interestingly, the hierarchical regulation of selenium and the distribution of selenoproteins metabolism is sex-specific (Kim et al., 2012). While selenium is regarded for its' potent antioxidant activity (Seale et al., 2018), a recent study on postmenopausal women links obesity and oxidative stress (Carvalho et al., 2015). Moreover, the researchers found that the dietary intake of selenium was significantly lower in obese postmenopausal women than that in lean women (Carvalho et al., 2015). However, the impact of menopause on the relationship between selenium and BMI has not been thoroughly investigated.

Selenium is abundantly present in the thyroid gland and catalyzes the conversion of inactive thyroid- T_4 to the active form-T_3 (Duntas, 2010). Because the thyroid plays an essential role in regulating basal metabolism, thermogenesis, and fat oxidation, thyroid function and body weight are closely linked (Longhi & Radetti, 2013). Notably, among overweight and obese adults with normal thyroid function, higher baseline free T3 and free T4 predicted more weight loss and maintenance (Liu et al., 2005). However, the impact of T3 on the relationship between selenium and BMI remains unknown and will be addressed by this dissertation study.

Physical activity plays an important role in energy expenditure and metabolism (Westerterp, 2013). Obesity-related research suggests that combining diet with physical activity and exercise, rather than diet alone, results in significant and clinically meaningful weight loss (Curioni & Lourenco, 2005; Johns et al., 2014; Nascimento et al., 2014;) Furthermore, several recent studies suggest a link between physical activity and selenium concentrations in the body (Letsiou et al., 2014; Margaritis et al., 2005; Zaitseva et al., 2015). Therefore, it is crucial to consider the potential effects of physical activity when investigating the relationship between selenium and BMI. This dissertation study will address the existing gaps in the literature, including the updated analysis of the relationship between serum selenium and BMI and the potential impact of menopausal status, T3, and PA in a nationally representative sample of US adults.

Theoretical Framework

The Homeostatic theory of obesity (HTO) has been selected to help facilitate and guide analysis and interpretation of findings and build a structured framework for this study. Developed in 2015 by British psychologist David Francis Marks, the theory proposes that imbalances can explain weight gain and obesity in homeostatic processes and the current obesogenic environment (Marks, 2015). The HTO (Figure 1) assumes that overconsumption of high-calorie, low-nutrient, and low-satiating foods, combined with social and environmental changes, is at the root of homeostasis imbalances and is the ultimate cause of obesity (Marks, 2015).

Expanding on the notion of physiological homeostatic, Marks (2015) introduces the concept of health based on the equilibrium of four mutually supportive and synergistic principal kinds: physiological, biochemical, psychological, and social. The disruption of one form of the regulatory process activates the response of another form and leads to obesity. Considering the relationship between selenium and BMI, including the potential impact of T3, PA, and menopausal status, the HTO explains how physiological and biochemical feedback mechanisms regulate billions of cells and thousands of reactions in the human body to help maintain a healthy and functioning metabolism.

Furthermore, the HTO informs about the factors which could potentially disrupt physiologic, environmental, and social homeostasis (or equilibrium) within the individual microsystem and contribute to obesity, including energy intake and expenditure, sex component, and the effects of psychological stressors. The HTO helps identify other factors which can disrupt healthy equilibrium and contribute to an obesogenic environment and weight gain. Drewnowski and Darmon (2005) reported that an inverse relationship exists between the energy density of foods and energy cost. Moreover, the inverse relationship between affordability and healthfulness explains why the highest rates of obesity and diabetes are found among the working poor (Marks, 2015). Therefore, other factors that can disrupt these mechanisms and be included in the study as control variables are income, race/ethnicity, and education level.

Ultimately, the HTO comprises several major homeostatic systems, including a system for moderating energy intake and expenditure, psychological dis-homeostasis, and the world's current socioeconomic disequilibrium. By encompassing the concepts of physiology, biochemistry, psychology, environment, and social structures under the lens of homeostasis and equilibrium, the HTO offers a unique and comprehensive framework for this dissertation study.

Statement of the Problem

The current research findings on the relationship between serum selenium and weight are conflicting, ranging from a significant inverse association between serum selenium and BMI (Zhong et al., 2018), no significant differences between obese and non-obese participants with regard to selenium (Ghayour-Mobarhan et al., 2005), a significant reduction in serum selenium level among morbidly obese female patients seeking bariatric surgery (Alasfar et al., 2011), a significant quadratic relationship with

BMI, being lower in individuals at the low and high ends of the BMI range (Combs et al., 2011), and the association of low serum selenium with overweight and obesity in premenopausal females (Kimmons et al., 2006). The current epidemic of obesity in the US calls for an updated analysis of the relationship between selenium and BMI and the impact of metabolically-active factors like T3 and PA in US adults. This research utilized the physical activity monitor data, which is more accurate than widely used self-reported data. The current obesity trends are especially troubling for women. This dissertation study is significant as it examines the cohort of women and how the relationship between selenium and BMI is affected by menopausal status. Importantly, the impact of demographic factors, including age, sex, race/ethnicity, income, education level, and daily caloric intake, was controlled for at each step of the analysis and included in the final report of the findings. This study is based on the novel obesity theory. This dissertation utilized a nationally representative sample of US adults.

This dissertation addresses the important gaps in the literature, including the lack of recent examination of the relationship between selenium and BMI, the potential moderating role of menopausal status in a nationally representative sample of female adults in the US, and the lack of analyzing the potential mediating roles of T3 and PA in the relationship between selenium and BMI in US adults.

Purpose and Objectives of the Study

This research study aims to expand the knowledge about the complex etiology of obesity by understanding the role of selenium in weight and the impact of menopausal status, T3, and PA in the relationship between selenium and BMI in US adults.

- **Aim One: A scoping review to map the currently available evidence on the serum selenium level and weight outcomes among US adults**:
  1. To investigate the relationship between selenium level and BMI in the adult population.
  2. To identify if the relationship between selenium level and BMI varies by sex.
  3. To determine the role of physical activity in the relationship between selenium level and BMI in the adult population.

- **Aim Two: Investigate the relationship between serum selenium, BMI, and the menopausal status in US adults:**
  1. To examine the relationship between serum selenium and BMI in US women.
  2. To control for the impact of race, age, income, education level, and daily caloric intake on the relationship between serum selenium and BMI in US women.
  3. To evaluate the role of menopause in the relationship between serum selenium and BMI in US women.

- **Aim Three: Analyze mediating effects of Triiodothyronine (T3) and Physical Activity (PA) in the selenium and BMI relationship in US adults:**
  1. To examine the role of T3 in the relationship between serum selenium level and BMI among US adults.
  2. To examine the role of PA in the relationship between serum selenium level and BMI among US adults.
  3. To control for the impact of sex, age, race, income, education level, and daily caloric intake on the role of T3 and PA in the relationship between serum selenium level and BMI among US adults.

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Appendix A (Chapter One Figures)

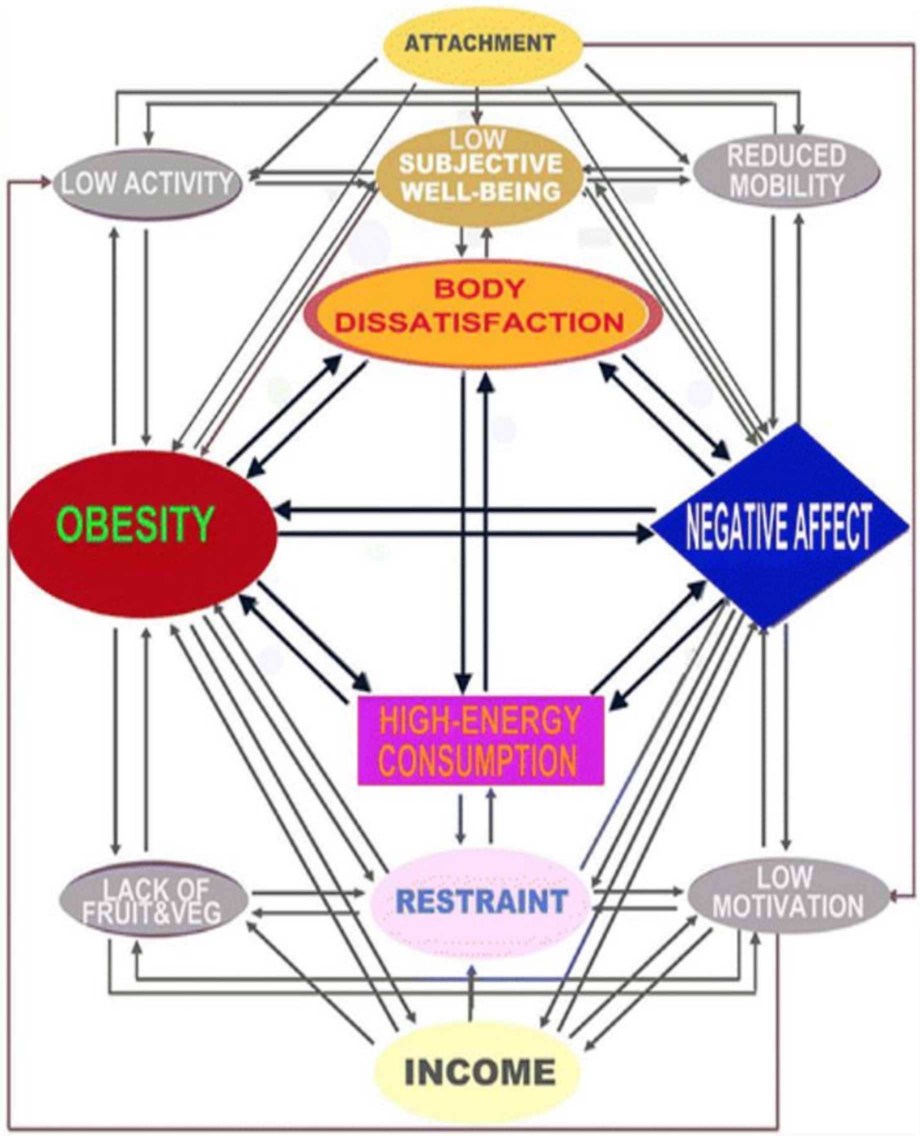

Fig.1.1 The Homeostatic Theory of Obesity: feedback loops in different homeostatic systems that maintain equilibrium become imbalanced.
Source: https://journals.sagepub.com/doi/full/10.1177/2055102915590692

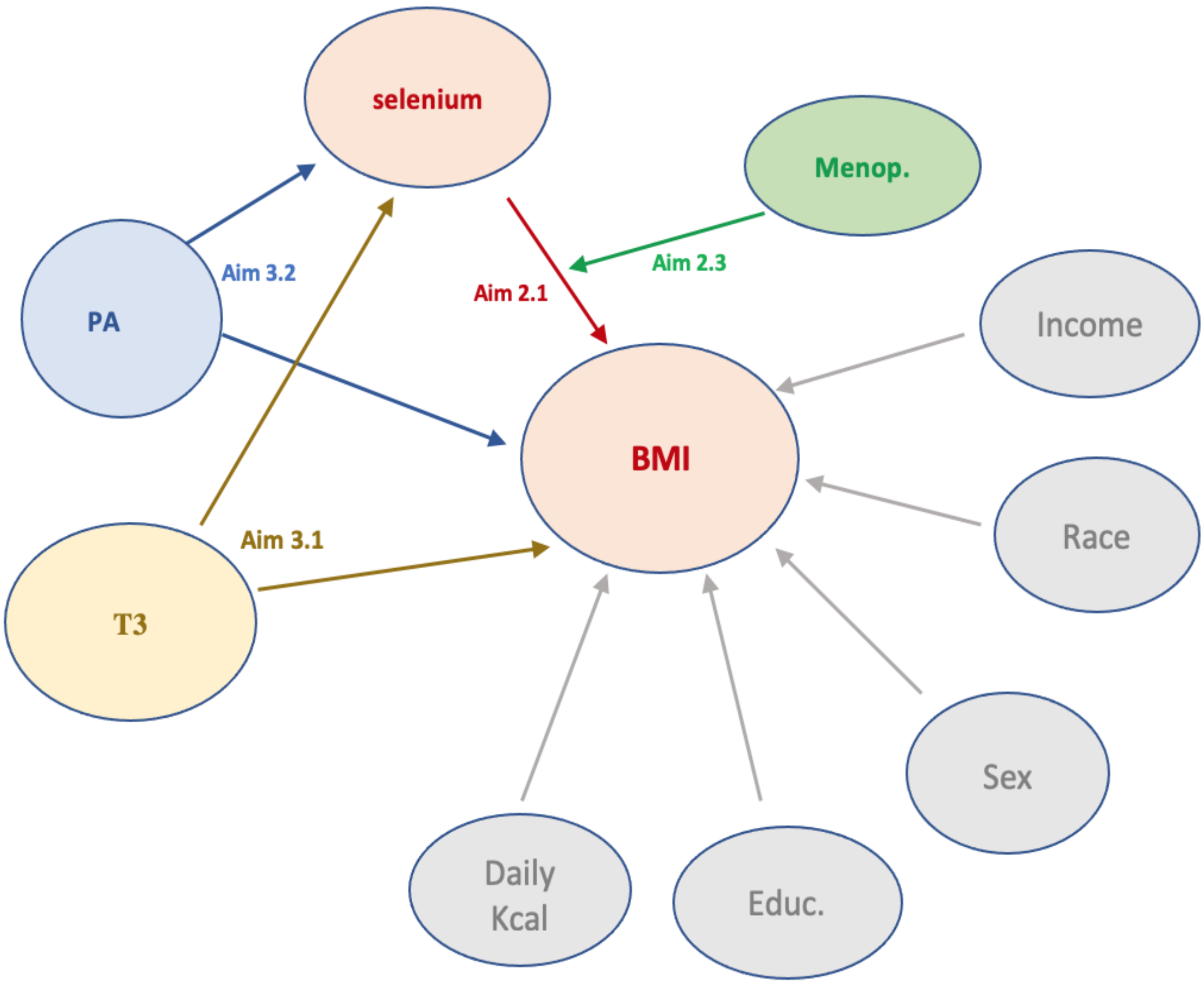

Fig 1.2 A Conceptual Framework of the Study (Adopted from the Homeostatic Theory of Obesity).

CHAPTER TWO

The relationship between serum selenium level, physical activity level, and BMI in the adult population: a scoping review

Abstract

Despite the extraordinary efforts of the scientific and medical communities, obesity remains a serious public health concern. At present, much attention is focused on the role of micronutrients in the current epidemic of obesity. Many questions about the functions of selenium and the role of physical activity in the relationship between blood selenium levels and body mass index (BMI) and whether this relationship is different by sex remain unanswered. This scoping review maps the currently available evidence on the serum selenium level and weight outcomes among US adults, highlighting conflicting results and a significant gap in the literature. Using Arksey and O'Malley's framework, the search included electronic bibliographic databases: PubMed, Embase, and Web of Science, as well as various grey literature sources published up to May 2020. Across nine included studies, there was considerable variation in sample size and characteristics, measures used, and results reported. Population size ranged from N=54 to N=17,030 participants. While the mechanisms underlying the associations of BMI with serum selenium concentrations are not entirely understood, the difference between males and females was evident in several studies included in this scoping review and warrants further investigation. This scoping review provides a range of publications on the relationship between selenium, physical activity, and BMI and identifies future research priorities in the field.

Keywords: Scoping review: adult: selenium: BMI: physical activity: micronutrient deficiency

Introduction

Across all demographics, obesity rates continue to rise in the United States (US) (CDC, 2021). Body Mass Index (BMI) is commonly used as a screening tool to assess overweight or obesity. Per CDC, 42.4% of US adults are obese, defined as BMI greater than 30, and 31.1 % of adults are overweight, with BMI between 25 and 29.9 (CDC, 2021). Although the prevalence of obesity is similar in women and men, 10% of adult women are considered to have extreme obesity (BMI > 40), double that of men (5.5 %) (NIH, 2020).

The direct medical cost of obesity and being overweight combined is approximately 10% of US health care spending (Tsai et al., 2011). The estimated annual medical cost of obesity for the non-institutionalized population of adults aged 18 and older in the US was $342.2 billion in 2013 (Biener et al., 2017). Additionally, the medical costs for people who are obese were $1,429 higher than those of "normal" weight (CDC, 2021).

Overweight and obesity significantly increase the risk for medical morbidity (Hruby & Hu, 2015), placing individuals at an increased risk for cardiovascular disease, high blood pressure, stroke, diabetes, obstructive sleep apnea, asthma, and high cholesterol, all of which are among the leading causes of death among adults in the US (CDD, 2021). Moreover, the International Agency for Research on Cancer (IARC) has identified 13 cancers associated with overweight and obesity, including meningioma, multiple myeloma, adenocarcinoma of the esophagus, and cancers of the thyroid, postmenopausal breast, gallbladder, stomach, liver, pancreas, kidney, ovaries, uterus, colon and rectum (colorectal) (WHO, 2016).

The issues surrounding obesity are multifactorial- several contributing factors play a role in the worsening epidemic of obesity, including certain micronutrients (Wang et al., 2016). A recent study by Wang et al. investigated dietary intake of selenium in association with anthropometric values, and the findings suggested that high dietary selenium intake is associated with a healthy weight, highlighting the importance of further analysis of blood Selenium levels in association with body weight (Wang et al., 2016).

Selenium is an essential trace mineral element that plays an essential role in adipocyte hypertrophy and abdominal fat accumulation (Kim et al., 2012). The results of several studies conducted in the last ten years suggested that selenium may play an essential role in thyroid hormone metabolism, reproductive health, cancer, inflammation, cardiovascular function, osteoporosis, diabetes, inflammation, and DNA synthesis (Alehagen & Aaseth, 2015; Karalis, 2019; Lewandowska et al., 2019; Sun et al., 2013; Oliva et al., 2019; Touat-Hamici et al., 2014 Wang et al., 2019).

Selenium is abundantly present in the thyroid gland and catalyzes the conversion of inactive thyroid- T4 to the active form-T3 (Duntas, 2010). Thyroid function and bodyweight appear to be closely correlated because the thyroid regulates basal metabolism (the rate of energy expenditure per unit time at rest) and thermogenesis and plays an active role in lipid and glucose metabolism fat oxidation (Longhi & Radetti, 2013). More specifically, among overweight and obese adults with normal thyroid function, higher baseline free T3 and free T4 predicted more weight loss and maintenance, suggesting the importance of thyroid hormones in body weight regulation and metabolism (Liu et al., 2005). The American Thyroid Association (ATA) reported that women are five to eight times more likely than men to have thyroid problems (ATA, 2017). Currently, there is limited evidence on the direct effect of selenium level on body weight. Moreover, there is a lack of studies synthesizing available evidence about the role of selenium on obesity in adults and whether the impact differs by sex.

Obesity-related research thus far suggests that diet combined with physical activity and exercise, rather than diet alone, results in a significant and clinically meaningful weight loss (Curioni & Lourenco, 2005; Johns et al., 2014; Nascimento et al., 2014;). Moreover, the Centers for Disease Control and Prevention recommends physical activity as one of the strategies to prevent obesity (CDC, 2016). Considering that several recent cross-sectional and interventional studies found a link between physical activity and selenium concentrations in the body (Letsiou, 2014; Margaritis et al., 2005; Zaitseva et al., 2015), it is important to evaluate the potential effects of physical activity when investigating the relationship between selenium and BMI, as well as the combined effect of blood selenium status and physical activity on body weight.

Considering there are a limited number of studies evaluating the relationship between selenium and BMI, and the results of those studies are inconsistent (Carvalho et al., 2016; Wang et a., 2016), a scoping review of existing studies designed to investigate the relationship between blood selenium and BMI, and include the potential effects of physical activity, is warranted. This scoping review aims to examine the published research about the relationship between blood selenium levels, average physical activity level, and BMI in adults and whether the relationships are different for women compared with men. This scoping review will identify research gaps and help to guide further research necessary to understand selenium's role in obesity and weight management.

Research Questions

The specific research questions of the review are:

1. What is the relationship between selenium level and BMI in the adult population?
2. Is the relationship between selenium level and BMI different by sex?
3. What is the role of physical activity in the relationship between selenium level and BMI in the adult population?

Methods

Due to the insufficient number of studies assessing the same outcome and significant heterogeneity of available literature, systematic review or meta-analytic pool were not feasible, and the scoping review format was conducted. This scoping review followed the guidelines outlined by Arksey and O'Malley (2005). It begins with identifying a broad research question. It follows by identifying relevant studies, selecting studies, abstracting data, and summarizing the results (including critical themes). Although a scoping review examines vast and diverse bodies of evidence and does not include an in-depth critical analysis of methodological data or quantitative data synthesis, an analysis of the quality of studies reviewed in this paper and synthesis of results is provided in this paper.

Search Strategy

A research librarian (W.E.) and primary investigator worked together to search the following four databases from January 1, 2010, through May 1, 2020: PubMed, Embase, and Web of Science. Several search terms were used including PubMed Search Terms: (selenium[major] OR selenium[ti] OR selenium[ot]) AND ("bodyweight" OR obesity OR "body composition" OR "Body Composition"[MeSH Terms] OR "Body Mass Index"[MeSH Terms] OR "Waist Circumference"[MeSH Terms] OR "Waist-Hip Ratio"[Mesh] OR "waist-hip") NOT (animals[mh] NOT humans[mh])

Embase Search Terms: 'selenium'/exp/mj AND ('body weight'/exp OR 'body weight' OR 'obesity'/exp OR obesity OR 'body composition'/exp OR 'body composition' OR 'body mass index'/exp OR 'body mass index' OR 'waist circumference'/exp OR 'waist circumference' OR 'waist-hip ratio'/exp OR 'waist-hip ratio')

Study Selection

The author of this scoping review (KD) screened titles and abstracts for eligibility. The full text of studies was assessed as relevant and was evaluated and read in full. Studies were included in the review if: 1) reported primary research, 2) described or evaluated serum selenium levels as well as weight measures and body composition, including percent body fat and BMI, and/or physical activity evaluation, 3) include non-hospitalized adults as study participants, 4) include "normal" weight, overweight and obese participants and/or those diagnosed with dyslipidemia 5) published in the English language between January 1, 2010, and May 1, 2020. The study designs were limited to quantitative analytic designs. Case studies and narrative reviews were excluded. Duplicate publications reporting the same outcome measurements were excluded.

Data Extraction

Data were extracted to a table and included author, year of publication, the origin of conduct, study design and settings, data source/population reach, sample size, statistical analysis, intervention if it is appropriated, serum selenium measures methodology, and outcomes, physical activity assessment and weight outcomes (Table 1). Study outcomes were tabulated with supporting data and organized according to the research questions. (Table 2).

Data Synthesis

Data syntheses were performed in several ways and displayed in the following sections: 1) Table1 presents a descriptive summary of the reviewed studies, including a study design, methods for measuring serum Selenium levels, the description of the intervention (when applicable), and the primary outcomes of interest for this review (BMI and weight measures); 2) A summary of evidence is provided in the Results and Discussion sections, including the quality of the design based upon the risk of bias. The heterogeneity of the nine reviewed studies and interventions precluded quantitative analyses or obtaining an overall effect size. Given the limited number of studies found on the topic and the fact that studies used different outcome measures and designs, we could not perform any statistical comparisons of the results. The results are described qualitatively and in evidence tables.

Methodological Quality of Included Studies

The ten items quality assessment tool developed by Cummings et al. (2008) was used to assess research design, sampling, measurement, and statistical analysis(29). Each item was assigned a score of one (met) or zero (not met). Each study was categorized based on the total points: high (7–10), medium (4–6), or low (0–3) quality. Table 3 provides the results of quality assessment scoring.

Results

Study characteristics

There was considerable variation in the methodological quality of included studies, from low (Cross-sectional analysis) to high (RCT) quality. Included studies were of varying quality based on study design, analytical tools, and sample size. Five studies were rated at 9 (high quality), and four were rated at 7, also high quality.

The studies included were all published from 2010 to 2020. Of 338 studies screened, 84 studies were reviewed. After removing duplicates (4 studies) and non-English articles (2 studies), ten studies reported the effect of dietary selenium intake on a range of body functions, including metabolism, arthritis, and weight (included in the analysis), nine studies included children or pregnant women, 52 studies focused on the effects of selenium on diabetes, various types cancers, HIV, PCOS, antioxidative properties of selenium, hypertension, alcoholism, depression, and micronutrient deficiencies and were removed from the scoping review, and were excluded. A total number of 9 studies met the inclusion criteria and were included in this scoping review (Figure 1): 5 out of 9 studies included PA measures, all nine studies included body weight as an outcome, while 8 of 9 studies analyzed blood selenium levels, and 1 out of 9 studies analyzed the dietary amount of selenium and its effect on weight. All studies reported the relationship between serum selenium and weight as measured by BMI (8 [88%]) or weight and % body fat (1 [11%]). Two studies were conducted in the United States, two in the UK, one in Kuwait, one in Canada, one in Brazil, one in China, and the United States. Seven studies included both men and women (7 [77%]), one study only enrolled women, and one included only men. Study sample size varied from N=54 to N=17,030 participants. Most studies used a cross-sectional design (4 [44%]), three used a prospective cohort study design, and two applied a prospective case-control study design. Most studies (8 [88%,]) did not apply any intervention, and one study [11%], included daily high-Se yeast supplements (300 mg/d) and a placebo group for 48 weeks (Hawkes et al., 2008).

Most of the studies were conducted within a community setting, and only two studies enrolled participants from a hospital/clinic setting. Two studies [33%] utilized the same dataset (NHANES III (1988 to 1994)) but applied different sample selection criteria, as well as outcome measures and analytical strategies. Eight studies reported BMI of the participants, while 7 [66%] studies also reported % body fat and waist circumference, and one study only reported body weight and % body fat. Six studies included physical activity measures.

Outcome measures

Most studies measured whole blood selenium concentrations using inductively coupled plasma mass spectrometry. This multi-element analytical technique is based on quadrupole inductively coupled plasma mass spectrometry ICP-MS technology- a highly reliable, validated, and specific method to measure the concentrations of trace minerals in blood serum utilized worldwide since 1983 (Tanner & Baranov, 1999; Thomas, 2003) Obesity status was estimated and categorized based on body mass index (BMI). BMI = weight in kilograms / (height in meters x height in meters). Most of the studies included in this scoping review applied a self-report to measure physical activity level in the participants.

The Relationship Between Selenium Level and BMI

A wide range of reported findings included:

- two studies reported a significant inverse association between serum selenium and BMI (Kimmnos et al., 2006; Zhong et al., 2018);
- one study found a significant positive correlation between plasma selenium and higher BMI (Carvalho et al., 2015);
- two studies reported no significant differences between obese and non-obese participants concerning selenium (Ghayour-Mobarhan et al., 2005; Zhong et al., 2018);
- one study found a significant reduction in serum selenium level among morbidly obese female patients seeking bariatric surgery (Alasfar et al., 2011);
- one study reported a significant quadratic relationship with BMI, being lower in individuals at the low and high ends of the BMI range (Combs et al., 2011);
- one study found a significant inverse association between plasma Se and waist circumference and a significant positive association between RBC Se and waist-to-hip ratio (Spina et a., 2013).

It is important to note that Wang et al. (2016) analyzed dietary (not serum) selenium in a prospective cohort study of 3.214 adults in Canada and discovered a significant negative association between dietary Se intake and obesity measurements independent of age, total dietary calorie intake, physical activity, smoking, alcohol, medication, and menopausal status (Wang et al., 2016).

Is the correlation between Selenium Level and BMI Different by sex?

Five out of nine studies included in this review provided information on the sex difference in the relationship between selenium level and body composition. One study found that the inverse association in serum Se comparing the highest with the lowest quartiles of BMI for BMI was very similar in men and women (Zhong et al., 2018). Interestingly, the associations between waist circumference and serum selenium concentrations were positive in men and virtually null in women, suggesting that general adiposity appeared to follow a different pattern of association with selenium compared to central adiposity between sexes (Zhong et al., 2018). One study reported that low selenium levels were associated with increasing BMI category among premenopausal women but not among men (Kimmons et al., 2006). And another study reported that participants with higher BMI, WC, or WHR were more likely to be older, be premenopausal, and have higher plasma Se (Spina et al., 2013). However, two studies found no significant difference in serum Se concentrations and BMI related to sex (Combs et al., 2011; Ghhayour-Mobarhan et al., 2005).

What is the role of physical activity in the relationship between selenium level and BMI in the adult population?

While none of the included studies evaluated the direct role of PA in the relationship between selenium level and BMI, five studies included PA measures in the overall analysis. One study found no significant correlation between serum Se and self-reported physical activity level(Ghhayour-Mobarhan et al., 2005). Similarly, another study did not report on the direct effect of PA on BMI but found that those with higher WHR were more likely to have lower RBC Selenium and physical activity (Spina et al., 2013).

Discussion

This scoping review identified the characteristics of the research to date, examining the relationship between blood selenium levels, physical activity level, and BMI in an adult population. Across nine included studies, there was considerable variation in sample size and characteristics, measures used, and results reported. Our scoping review found that the reported relationship between selenium level and BMI in the adult population varied significantly among included studies, ranging from positive correlation, no correlation, and inverse correlation. Specifically, six studies reported a negative association between selenium level, BMI, and other weight measures. In contrast, the other three studies found no relationship or positive association between selenium level and weight measures. Similarly, studies on the relationship between selenium level and BMI between sexes found inconsistent findings. Limited studies examined the influence of physical activity in the relationship between selenium level and BMI in the adult population.

This review found mixed results on the relationship between selenium and weight in an adult population. One of the possible reasons is serum selenium assessment. Serum selenium data needs to be analyzed with caution, as it demonstrates not only selenium intake but also other underlying conditions that could modify serum selenium concentrations (Zhong et al., 2018). The mechanisms underlying the association between selenium and BMI are still unknown (Zhong et al., 2018). Therefore, it is possible that in a non-hospitalized adult population with minor variations within the normal range of selenium, physiological effects such as BMI may not be statistically noticeable or consistent.

Furthermore, although a BMI is the most widely used measure of obesity, its' accuracy, validity, and specificity are limited (Collazo-Clavell et al., 2008; Kennedy et al., 2009; Rahman et al., 2010) and may not represent an accurate picture of adiposity status and metabolic health. Given that the populations included in these studies are also different in sample characteristics and sample size with various measurements used, this could also contribute to the inconsistent findings across these studies. The existing studies on the relationship between selenium and BMI are conflicting and contradictory, highlighting the importance of investigating the topic further via various scientific methods.

In terms of sex difference, the five studies which provided conflicting information on the sex difference for the relationship between selenium level and body compositions varied in design, sample size, and findings. Two out of five studies did not find differences related to sex, while three studies reported significant differences. While the findings varied significantly among the studies, women seem to be at a greater risk for selenium-related weight changes (Kimmons et al., 2006; Spina et al., 2013), which is in accordance with the theory that the hierarchical regulation of selenium metabolism under the condition of low selenium levels is sex-specific, and the distribution of melanoproteins differs significantly between sex (Leisiou et al., 2014).

Selenium is abundantly present in the thyroid gland and catalyzes the conversion of inactive thyroid- T4 to the active form-T3 (Duntas, 2010). Thyroid function and bodyweight appear to be closely correlated because the thyroid regulates basal metabolism (the rate of energy expenditure per unit time at rest) and thermogenesis and plays an active role in lipid and glucose metabolism fat oxidation (Longhi & Radetti, 2013). More specifically, among overweight and obese adults with normal thyroid function, higher baseline free T3 and free T4 predicted more weight loss and maintenance, suggesting the importance of thyroid hormones in body weight regulation and metabolism (Liu et al., 2017). Because women are significantly (seven to ten times) more likely than men to suffer from thyroid problems (ATA, 2017), evaluating the sex-specific role of selenium and thyroid measures on BMI is essential. Furthermore, animal experiments suggested that estrogen status affects tissue distribution and metabolism of selenium by modulating Sepp1, a protein that regulates selenium transport (Zhou et al., 2012). Nevertheless, the role of sex on selenium and BMI has not been thoroughly investigated, and the results included in this review are conflicting. This highlights the importance of further scientific investigations into the role of sex in the selenium and BMI relationship.

Multiple previous studies recognized the importance of selenium in thyroid function (Ventua et al., 2017; Wichman et al., 2016) and, therefore, body metabolism, so it is essential to explore novel strategies for including other metabolism-effecting measures like PA adjusted by a total daily calorie intake. The role of physical activity as a mediator between selenium level and body weight remains unclear. Most of the studies that measured self-reported physical activity levels did not report or discuss the possible role physical activity played in the outcomes, preventing any conclusions from being drawn regarding the effects of physical activity. While CDC recommends physical activity to prevent obesity (CDC, 2021), it has been widely suggested that diet combined with physical activity and exercise, rather than diet alone, results in significant and clinically meaningful weight loss (Curioni & Lourenco, 2005; Johns DJ, Hartmann-Boyce, et al., 2014; Nascimento et al., 2014). Additionally, several recent studies found a link between physical activity and selenium concentrations in the body (Letsiou et al., 2014; Margaritis et al., 2005; Zaitseva et al., 2015). Ultimately, physical activity plays a direct role in energy expenditure and metabolism (Margaritis et al., 2005). Therefore, the role of PA needs to be explored closely, and the mediating effect on BMI evaluated while the total daily caloric intake is taken into consideration and adjusted for.

Limitations

To this author's best knowledge, this is the first scoping review that has attempted to examine and summarize the existing evidence about the relationship between selenium and BMI. Furthermore, this is the first scoping review to compare how the relationship between selenium and BMI is affected by PA and whether this relationship is different by sex. There were several limitations to this review. First, this scoping review presented an overview of the relationship of blood selenium level and weight in generally healthy non-selenium-deficient adults, limiting the findings' generalizability to other groups, including those with chronic or acute disorders and mineral-deficient individuals. Lastly, the search strategy applied to this scoping review may not have been sensitive enough to capture the full breadth of research activities, which included the analysis of the association between serum selenium and body weight. It is also important to acknowledge that most studies were of varying quality based on study design, sample size, intensity, analytical approaches, and results.

Recommendations for future research

This systematic review observed and summarized inconsistent findings on the relationship between serum Selenium level, PA and BMI. To better understand the influence of selenium on BMI, several significant gaps in knowledge have been identified, and recommendations to enhance the research process are offered. First, future studies should evaluate PA's role in the relationship between selenium level and BMI. Considering the role PA plays in energy expenditure and overall metabolism, evaluating the role of PA in the relationship between selenium and BMI is crucial. Additionally, several contributing factors need to be factored into a future analysis, including total daily caloric intake, overall activity level, neighborhood walkability, and employment (sedentary) status. Furthermore, considering that dietary Se intake undergoes significant variability worldwide because of its content in the soil and the diversity of eating habits(Carvalho et al., 2015), to identify groups at risk for food insecurity, high-selenium food availability, affordability, and daily consumption needs to be investigated. Future research should identify additional factors that contribute to the relationship between selenium and BMI.

Conclusions

Overweight and obesity are a public health concern and alarming issue. The obesity epidemic is causing significant health, quality of life, financial and social ramifications on a community at large. This scoping review provides a synthesis of current publications on the serum selenium level and weight outcomes among adults, highlighting conflicting results and significant gaps in the literature. While the mechanisms underlying the associations of BMI with serum selenium concentrations are not entirely understood, the difference between males and females was reported by two studies (Combs et al., 2011; Spina et al., 2013). included in this scoping review and warrants further investigation.

Most importantly, the consideration of PA in the relationship between selenium and BMI needs to be evaluated. Considering the role of selenium in thyroid gland health and overall metabolism, the PA and its' role in energy expenditure, metabolism, and the possible effect on the weight outcomes cannot be overlooked. Addressing these research gaps may provide policymakers, nutritionists, and healthcare providers with the necessary scientific evidence to make informed decisions regarding the role of selenium in obesity prevention and treatment.

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Appendix B (Chapter Two Tables and Figures)

Table 2.1 Study and participant characteristics and outcomes

Author (Year)	Design & Settings	Data Source/ Sample Reach	Statistical Analysis Intervention	Se measures	Physical Activity Assessment	Outcomes
Alasfar et al., (2011)	**Prospective Case-Control Study** **Kuwait**	N=40 morbidly obese female patients (BMI ≥ 40) seeking bariatric surgery as a treatment for their condition. N= 44- control group female patients with BMI ≤30	A Student's t test was used for comparison of the two groups. P < 0.05 was considered as statistically significant **No intervention**	Selenium standards were prepared in 0.1% hydrochloric acid (HCL) and run in the range of 30–90 ppb. A modifier (20 mg citric acid in 2 ml palladium 500 ppm) was used in analyzing serum selenium.	Not measured	For morbidly obese patients, the serum level of copper, zinc, selenium, and magnesium was 1,623.84, 698.34, 86.08, and 17,830 mg/l, respectively, compared to 1,633.36, 734.82, 101.14, and 18,260 mg/l for the control group. The serum levels of the trace elements were not statistically significantly different between the two groups except for selenium, which was significantly reduced among morbidly obese female patients (p<0.0001).
Carvalho et al., (2015)	**Cross-sectional study** **Brazil**	N=83 dyslipidemia and hypertensive patients (49 males and 34 females) Patients were considered dyslipidemic if they were using a lipid-lowering medication or were found to have serum LDL ≥ 160 mg/dL or trigly-cerides ≥ 150mg/dL or if high-density lipoprotein (HDL) levels were < 40 mg/dL in men and < 50mg/ dL in women.	Kolmogorov-Sminorv statistical test used to assess normality of the variables. Spearman test – to analyze the association between Se intake and the variables under study. Kruskal-Wallis test with a post- hoc Mann-Whitney U test to compare between the two groups to check for associations between the plasma Se concentrations in tertials of the sample population and thyroid hormones and anthropometric variables. A P value < 0.05 was considered statistically significant No intervention	Se analyzed in samples collected in VACUETTE® Trace Elements NH Sodium Heparin tubes and kept at -70°C until the moment analysis was performed by atomic absorption spec-trometry using a mass spectrometer with an inducti- vely coupled plasma source. Habitual dietary Se intake was assessed using a food frequency questionnaire.	Questionnaires were employed to assess physical activity. Individuals were classified as either sedentary, if they practiced no physical activity, or moderately inactive, since none of them was found to expend more than 100 kcal of energy through physical activity per day	Patients with plasma Se ≥ 95 µg/L were found to have a higher BMI (30.74 ± 4.31 vs 27.68 ± 5.63 kg/m^2, P = 0.02) and waist-to-height ratio (0.65 ± 0.05 vs 0.59 ± 0.07, P = 0.003) when compared to those with concentrations between 80 and 94 µg/L. Se intake associated positively with T_3L/T_4L ratio (r = 0.273; P= 0.03), BMI (r= 0.257, P= 0.04) and WC (r= 0.299, P= 0.02).

Author (Year)	Design & Settings	Data Source/ Sample Reach	Statistical Analysis Intervention	Se measures	Physical Activity Assessment	Outcomes
Combs et al., (2011)	**Prospective Cohort Study** **USA**	N= 261 healthy subjects over 18 yrs., (106 men, 155 women)	Pearson and Spearman correlations, regression analysis, ANOVA, non-parametric dis- criminate analysis, Tukey contrast and orthogonal contrast **No intervention**	Selenium status was assessed on the basis of the activity of GPX and the amount of SEPP1 in serum, and the amounts of Se in plasma, buccal cells and urine	Not measured	Serum SEPP1, but not GPX3 activity or total plasma Se, showed a significant quadratic relationship with body mass index (BMI) ($r^2 = 0.054$, $P < 0.002$), being lower in individuals at the low and high ends of the BMI range. Comparing the means of the 3 groups, the mean of the lowest BMI group was highly significantly less than the mean of the overweight group, p = 0.0008 An orthogonal contrast test showed a significant quadratic trend in the means of the 3 groups, p = 0.003. The back-transformed SEPP1 means (± 1 S.D.) are as follows: BMI < 25: 3.17 (3.07-3.26); BMI 25-30: 3.69 (3.59-3.80); BMI > 30: 3.46 (3.36-3.58).
Ghayour-Mobarha n et al., (2005)	**Prospective cohort study** **UK**	N=189 adult subject (95 =men, 94 = women) 41=obese (BMI >30), 6= metabolic syndrome	Normality assessment by the Kolmogorov--Smirnov test. Categorical data compared using Fisher's exact or w^2 tests. Stepwise multiple regression analysis used to predict whether serum trace elements were related to dietary trace elements and traditional coronary risk factors: age, sex, BMI, smoking, fasting glucose and lipid pro¢le, and systolic and diastolic blood pressure (DBP). A P <0.05 was considered significant **No intervention**	Se determined by electrothermal atomic absorption spectrometry with Zeeman background correction using a palladium chloride chemical modifier.	Self-reported habitual physical activity	No significant differences found between obese and non- obese subjects with regard to selenium Lower serum GPx concentrations in obese men compared to non-obese subjects was found Selenium did not differ significantly between men and women (P<0.05) Women aged between 50--59 years had significantly higher serum selenium compared with the group aged 70 years or more. Serum selenium concentrations were predicted by serum total cholesterol (P<0.01), serum CRP concentrations (P<0.05) and dietary selenium (P<0.03). Dietary copper was positively associated with serum selenium (P<0.04).

Author (Year)	Design & Settings	Data Source/ Sample Reach	Statistical Analysis **Intervention**	Se measures	Physical Activity Assessment	Outcomes
Hawkes et al., (2008) **USA**	**RCT** **USA**	N=54 healthy men, aged 18-45	Power estimation-the Box–Cox A first-order autoregressive covariance structure - to account for the dependencies among the repeated measures. Single degree of freedom contrasts -to compare the baseline averages with the treatment and follow-up for two groups. The Bonferroni adjustment for multiplicity was applied Adjusted P< 0.05 were considered significant **Intervention**: daily high-Se yeast supplements (300 mg/d) or placebo for 48 weeks	Fasting serum Se concentrations were measured by HPLC of the fluorescent derivative formed from reaction with diami- nonaphthalene after digestion in a (5:2, v/v) nitric–perchloric acid mixture. No analysis of Serum Se & weight reported by the study	During 3-d period subjects wore a heart-rate monitor and recorded all physical activities every 60min. The estimated energy expended in each activity was summed to obtain a daily value, and the 3 daily values were averaged to estimate the energy expended per day in voluntary activities at each point in the study	Body weight increased in both groups during the 48-week treatment period and remained elevated for the 48-week follow-up period. Body fat increased by 1.2 kg in both groups. Energy intake and voluntary activity levels were not different between the groups and remained unchanged during the treatment period
Kimmons et al., (2006)	**Cross-section analysis** **USA**	NHANES III (1988 to 1994) N= 16,191 adults ≥ 19 years with BMI ≥ 18.5 (8,383 women, 7,808 men)	Odds Ratios (OR) and corresponding 95% confidence intervals (CI) for low vs sufficient levels of each biomarker, using logistic regression to adjust for age, race/ethnicity, hormone therapy/oral contraceptive use (women), and serum cotinine concentration (continuous). Tests were determined to be statistically significant at a *P* value of .05. **No intervention**	inductively coupled plasma-mass spectrometry The cutoff value signifying low selenium of < 100 ug/L	Not included in analyses	Low serum Se, defined as o100 mg/L (o1.27 mmol/L), was associated with overweight and obesity in premenopausal females Among premenopausal women, increasing BMI category was associated with low biochemical micronutrient levels for vitamin E, alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein/zeaxanthin, lycopene, total carotenoids, vitamin C, selenium (premenopausal), vitamin D, and folate Among men aged 19.0–64.9 years, increasing BMI category was associated with low biochemical micronutrient levels for alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein/zeaxanthin, total carotenoids, vitamin C, selenium, and folate

Author (Year)	Design & Settings	Data Source/ Sample Reach	Statistical Analysis Intervention	Se measures	Physical Activity Assessment	Outcomes
Spina et al., (2013)	**Cross-section analysis** **UK**	2000–2001 National Diet and Nutrition Survey N=1045 (577 females, 468 male) British Caucasian adults ages 19–64 randomly selected from 152 areas in Great Britain	Bivariate analysis was performed by anthropometric indices to test for potential confounders. nonparametric Kruskal–Wallis was used for continuous variables and Pearson χ^2 for categorical variables. Multivariate linear regression was performed to estimate adjusted mean differences (95% CI) **No intervention**	Non-fasting plasma and whole-blood Se concentrations were measured by inductively coupled plasma mass spectrometry	Records of duration and intensity of physical activity enabled calculation of a physical activity score as an indication of energy expenditure (h kcal/min),	A significant inverse association was observed between plasma Se and WC as well as a significant positive association between RBC Se and WHR at full adjustment. Similar results, though mostly not statistically significant, were observed in sex and menopausal-status subgroup analyses. In bivariate associations, participants with higher BMI, WC, or WHR were more likely to be older (p o 0.001); be premenopausal (females; p o 0.001); have higher plasma Se (p =0.007) In fully adjusted multivariate models, in the overall sample, higher BMI was associated with significantly decreased whole- blood GPx activity, with an adjusted mean difference (95% CI) of 7.9 (13.2, 2.7) nmol mg Hb^1 min^1 between obese and normal-weight participants; nonsignificant decreases were observed for plasma and RBC Se with increasing BMI.
Zhong et al., (2018)	**Cross-section analysis** **USA & China**	NHANES III (1988 to 1994) N=17,030 Adult individuals aged 20 years and older Men (*n* = 6,440) Women (*n* = 6,849)	Multivariable linear regression w/95% (CI) used to calculate the difference in serum selenium comparing BMI, %BF, and WC quartiles to the first quartile analyzed stratified by sex **No intervention**	Fasting serum Se measured by Zeeman atomic absorption spectrometry The limit of detection - 8 ng/mL	Based on interview questionnaires, physical activities were coded and classified according to the rate of energy expenditure.	For BMI, the inverse association in serum Se comparing the highest with the lowest quartiles of BMI was -4.0 (-5.5, -1.6) ng/mL in both men and women. For %BF, the average differences in serum Se between the highest and the lowest quartiles of %BF were -1.7 (-4.2, 0.7) ng/mL in men and -4.5 (-7.0, -1.9) ng/mL in women. For WC, the average differences in serum Se between the highest and the lowest quartiles were -1.9 (-3.8, -0.1) ng/mL in men and -3.9 (-5.8, -2.0) ng/mL in women.

Author (Year)	Design & Settings	Data Source/ Sample Reach	Statistical Analysis Intervention	Se measures	Physical Activity Assessment	Outcomes
Wang et al., (2016)	**Prospective cohort study** **Canada**	N= 3214 of (>19 years of age) adults without chronic conditions. Women (n=2295) and men (n=919).	Anthropometrics, body composition, dietary intake and physical activity were compared between men and women using independent student's *t*-test. Partial correlation analysis controlling for age, total calorie intake, and physical activity was subsequently applied to determine the correlation between dietary Se intake and obesity measurements Stepwise multiple linear regression analysis was used to evaluate the contribution of dietary Se intake to obesity among women or men. **No intervention**	Dietary Se intake was analyzed by analysis of variance and covariance controlling for age, total calorie intake and physical activity. Analyses on obesity measurements were performed when participants were divided into tertiles (low, medium, or high) based on dietary Se intake using analysis of variance and covariance controlling for age, total calorie intake and physical activity.	Physical activity patterns were measured using the ARIC Baecke Questionnaire, which consists of a Work Index, Sports Index, and Leisure Time Activity Index	Obese men and women had the lowest dietary Se intake, being 24% to 31% lower than corresponding normal weight men and women, classified by both BMI and body fat percentage. Subjects with the highest dietary Se intake had the lowest BMI, waist circumference, and trunk, android, gynoid and total body fat percentages, with a clear dose-dependent inverse relationship observed in both sex groups. Significant negative associations discovered between dietary Se intake and obesity measurements were independent of age, total dietary calorie intake, physical activity, smoking, alcohol, medication, and menopausal status.

Table 2.2 Study outcomes by research questions: **1.** What is the relationship between selenium level and BMI in adult population? **2.** Is relationship between selenium level and BMI different by sex? **3.** What is the role of physical activity in the relationship between selenium level and BMI in adult population?

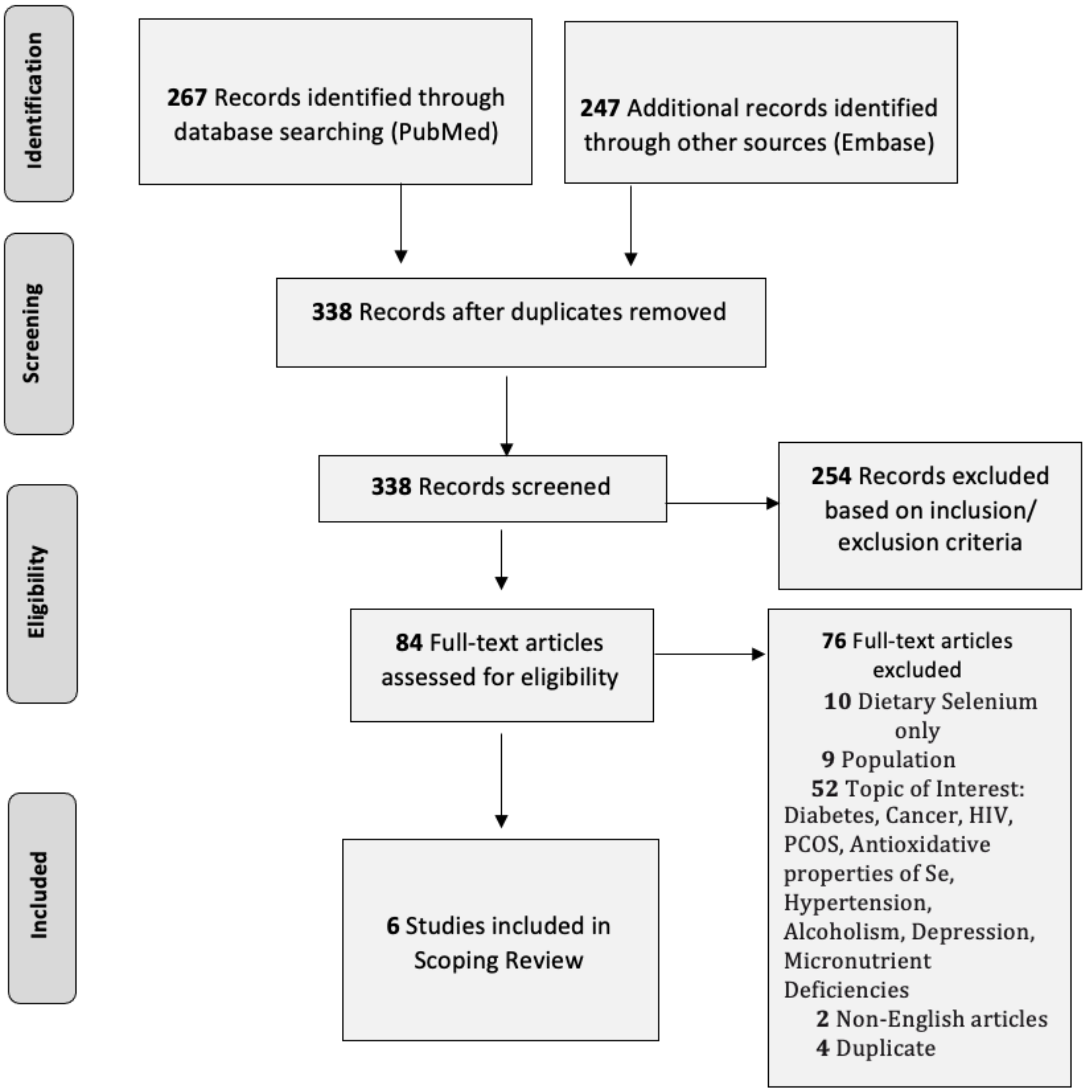
Author (Year)	Weight Outcomes	Sex Differences	Physical Activity Outcomes
Alasfar et al., (2011)	For morbidly obese patients, the serum level of copper, zinc, selenium, and magnesium was 1,623.84, 698.34, 86.08, and 17,830 mg/l, respectively, compared to 1,633.36, 734.82, 101.14, and 18,260 mg/l for the control group.	Women only	Not measured
Carvalho et al., (2015)	Patients with plasma Se ≥ 95 µg/L were found to have a higher BMI (30.74 ± 4.31 vs 27.68 ± 5.63 kg/m^2, P = 0.02) and waist-to-height ratio (0.65 ± 0.05 vs 0.59 ± 0.07, P = 0.003) when compared to those with concentrations between 80 and 94 µg/L.	No sex differences reported	Used in descriptive statistical analysis only. Individuals were classified as either sedentary, if they practiced no physical activity, or moderately inactive, since none of them was found to expend more than 100 kcal of energy through physical activity per day.
Combs et al., (2011)	Serum SEPP1, but not GPX3 activity or total plasma Se, showed a significant quadratic relationship with body mass index (BMI) (r^2 = 0.054, P < 0.002), being lower in individuals at the low and high ends of the BMI range. Comparing the means of the 3 groups, the mean of the lowest BMI group was highly significantly less than the mean of the overweight group, p = 0.0008 An orthogonal contrast test showed a significant quadratic trend in the means of the 3 groups, p = 0.003.	Both men and women in study showed a significant quadratic relationship with BMI, being lower in individuals at the low and high ends of the BMI range with no major sex differences reported. No sex differences reported.	Not measured
Ghayour-Mobarhan et al., (2005)	No significant differences found between obese and non- obese subjects with regard to selenium Serum selenium concentrations were predicted by serum total cholesterol (P<0.01), serum CRP concentrations (P<0.05) and dietary selenium (P<0.03). Dietary copper was positively associated with serum selenium (P<0.04).	Lower serum GPx concentrations in obese men compared to non-obese subjects was found Selenium did not differ significantly between men and women (P<0.05) Women aged between 50--59 years had significantly higher serum selenium compared with the group aged 70 years or more.	no significant correlation between serum Se and physical activity and did not analyze the relationship between physical activity level and BMI.
Hawkes et al., (2008) **USA**	Body weight increased in both groups during the 48-week treatment period and remained elevated for the 48-week follow-up period. Body fat increased by 1.2 kg in both groups. Energy intake and voluntary activity levels were not different between the groups and remained unchanged during the treatment period	Evaluated men only	energy intake and physical activity levels were not different between the groups and remained unchanged during the treatment period. However, the effect of physical activity on the overall result (BMI, weight measures) were not reported.

Author (Year)	Weight Outcomes	Sex Differences	Physical Activity Outcomes
Kimmons et al., (2006)	Low serum Se, defined as o100 mg/L (o1.27 mmol/L), was associated with overweight and obesity in premenopausal females Among premenopausal women, increasing BMI category was associated with low biochemical micronutrient levels for vitamin E, alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein/zeaxanthin, lycopene, total carotenoids, vitamin C, selenium (premenopausal), vitamin D, and folate	Among men aged 19.0–64.9 years, increasing BMI category was associated with low biochemical micronutrient levels for alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein/zeaxanthin, total carotenoids, vitamin C, selenium, and folate	Not measured
Spina et al., (2013)	A significant inverse association was observed between plasma Se and WC as well as a significant positive association between RBC Se and WHR at full adjustment. In fully adjusted multivariate models, in the overall sample, higher BMI was associated with significantly decreased whole- blood GPx activity, with an adjusted mean difference (95% CI) of 7.9 (13.2, 2.7) nmol mg Hb^{1} min^{1} between obese and normal-weight participants; nonsignificant decreases were observed for plasma and RBC Se with increasing BMI.	Similar results, though mostly not statistically significant, were observed in sex and menopausal-status subgroup analyses. In bivariate associations, participants with higher BMI, WC, or WHR were more likely to be older (p o 0.001); be premenopausal (females; p o 0.001); have higher plasma Se (p =0.007)	did not report on direct effect of PA on BMI but applied physical activity score (records of duration and intensity) as an indication of energy expenditure and found that those with higher WHR were more likely to have lower RBC Selenium and physical activity.
Zhong et al., (2018)	For BMI, the inverse association in serum Se comparing the highest with the lowest quartiles of BMI was -4.0 (-5.5, -1.6) ng/mL in both men and women. For %BF, the average differences in serum Se between the highest and the lowest quartiles of %BF were -1.7 (-4.2, 0.7) ng/mL in men and -4.5 (-7.0, -1.9) ng/mL in women.	For WC, the average differences in serum Se between the highest and the lowest quartiles were -1.9 (-3.8, -0.1) ng/mL in men and -3.9 (-5.8, -2.0) ng/mL in women. For %BF, the average differences in serum Se between the highest and the lowest quartiles of %BF were -1.7 (-4.2, 0.7) ng/mL in men and -4.5 (-7.0, -1.9) ng/mL in women.	Analyzed as a cofounding factor. coded and classified physical activity according to the rate of energy expenditure. Leisure-time physical activity in the past month was ascertained during the home interview. Sedentary lifestyle was defined as no moderate or vigorous physical activities performed in the past month.
Wang et al., (2016)	Subjects with the highest dietary Se intake had the lowest BMI, waist circumference, and trunk, android, gynoid and total body fat percentages, with a clear dose-dependent inverse relationship observed in both sex groups. Significant negative associations discovered between dietary Se intake and obesity measurements were independent of age, total dietary calorie intake, physical activity, smoking, alcohol, medication, and menopausal status.	Obese men and women had the lowest dietary Se intake, being 24% to 31% lower than corresponding normal weight men and women, classified by both BMI and body fat percentage.	PA was used with Partial correlation analysis to determine the correlation between dietary Se intake and obesity measurements controlling for physical activity, but not evaluating the role PA independently.

Table 2.3: Quality Assessment Scoring

Author (Year)	Design Probability Sampling	Sampled From more than one site?	Sample size Justified?	Anonymity Protected	Response rate greater than 60%?	Weight measured other than BMI?	Weight Measure validated?	Theoretical Framework?	If multiple outcomes studied, correlation analyzed?	Covariates & confounders controlled for?	Total
Alasfar et al., (2011)	0	0	1	1	1	1	1	0	1	1	7
Carvalho et al., (2015)	0	0	1	1	1	1	1	0	1	1	7
Combs et al., (2011)	1	1	1	1	1	1	1	0	1	1	9
Ghayour-Mobarhan et al., (2005)	0	0	1	1	1	1	1	0	1	1	7
Hawkes et al., (2008)	0	0	1	1	1	1	1	0	1	1	7
Kimmons et al., (2006)	1	1	1	1	1	1	1	0	1	1	9
Spina et al., (2013)	1	1	1	1	1	1	1	0	1	1	9
Zhong et al., (2018)	1	1	1	1	1	1	1	0	1	1	9
Wang et al., (2016)	1	1	1	1	1	1	1	0	1	1	9

1 = met criteria, 0 = did not meet criteria. Adapted from Cummings et al., (2008). Copyright 2014 by Sage Publication



Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed10000

Fig. 2.1 Selection of sources of evidence in this review using the original PRISMA statement

Study conceptual framework diagram

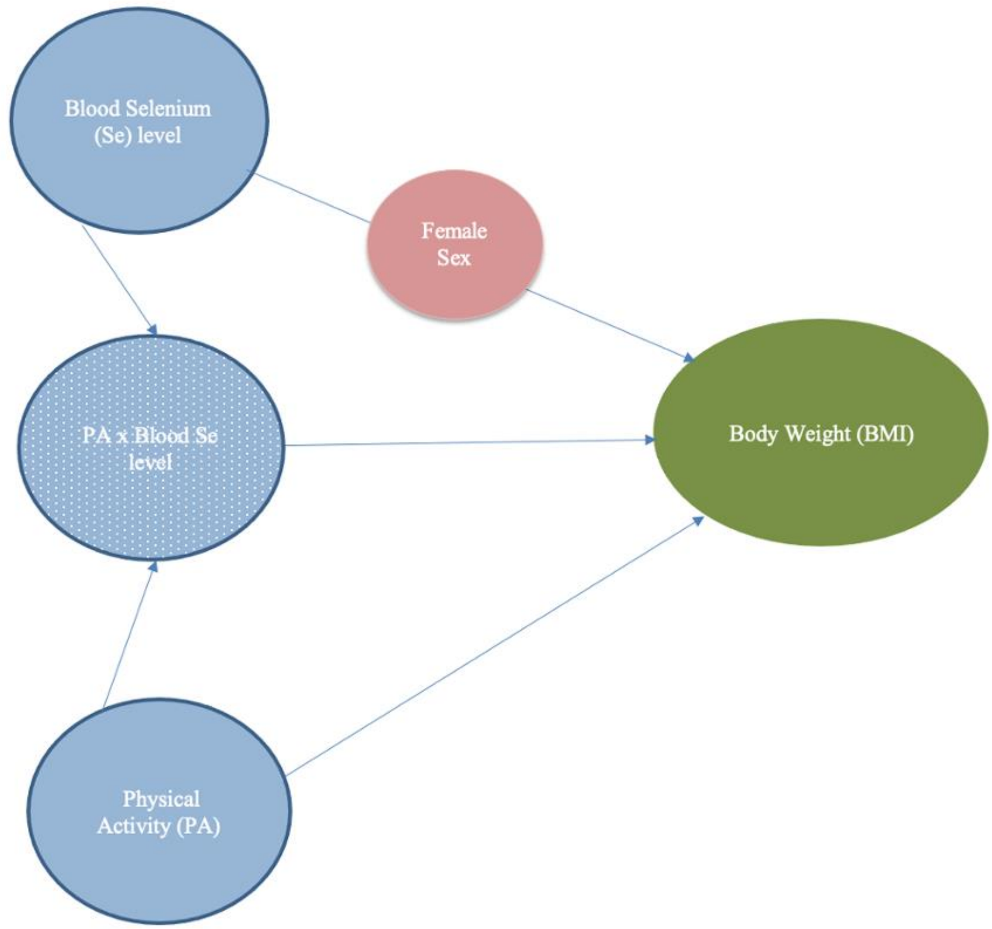


Fig. 2.2 Conceptual framework diagram adopted from The Circle of Disconnect Model by David Marks.

CHAPTER THREE

Is the Relationship Between Serum Selenium and BMI Different by Menopausal Status and Demographic Factors in US women?

Abstract

Background

Obesity, defined by the Body Mass Index (BMI), has reached epidemic proportions. Numerous physiological functions related to the body's metabolism, reproduction, and antioxidant activity have been attributed to selenium. However, data concerning the association of serum selenium and BMI in menopausal women are limited. The study aimed 1) to investigate the relationship between serum selenium and BMI in US women, 2) to explore the impact of race, age, income, education level, and daily caloric intake on the relationship between serum selenium and BMI, and 3) to evaluate the role of menopause in the relationship between serum selenium and BMI.

Methods

A cross-sectional study design utilizing US National Health and Nutrition Examination Survey (NHANES 2011-2012) was used to examine the associations between serum selenium, menopause, and BMI. A total sample of 2,130 women aged ≥20 years were included in the analysis based on the blood samples reporting serum selenium data and BMI values from physical examination results. Sell-reported menopausal status was detected in 767 female participants. Dietary data from two days were available for 1,943 participants. Income data were available for 2,055 participants and education data were available for all 2,130 participants. Descriptive statistics, t-test, and multiple linear regression models were applied for analysis.

Results

After adjusting for demographic factors, no statistically significant relationship between serum selenium and BMI was detected among US women. The impact of race, age, income, education level, and daily caloric intake on the relationship between serum selenium and BMI was not statistically meaningful. Postmenopausal women had a statistically higher mean BMI (30.5) vs. 28.9 in a premenopausal group, while mean daily caloric intake was lower in postmenopausal women (1680kcal) compared to premenopausal women (1900kcal). Mean serum selenium did not statistically differ between the two groups. The menopausal status did not moderate the effect of serum selenium on BMI.

Conclusion

In a nationally representative sample of US female adults, no statistically significant relationship was detected between serum selenium and BMI in the years 2011-2012. Furthermore, menopausal status and demographic factors did not influence the relationships between serum selenium and BMI. Other metabolically significant factors (e.g., thyroid hormones or physical activity) need to be explored for future research.

Keywords: Selenium, BMI**,** Women**,** Menopause**,** Metabolism

1. Introduction

Despite the great efforts of the scientific and medical communities, the prevalence of obesity continues to increase (CDC, 20201). Body mass index (BMI) is commonly used as a screening tool to define overweight or obesity. Almost 40% of US adults are obese, defined as BMI greater than 30, and 32% of adults are overweight, with BMI between 25 and 29.9 (CDC, 2021). Obesity significantly increases the risk for medical morbidity (CDC, 2017), placing individuals at an increased risk for cardiovascular disease, high blood pressure, stroke, diabetes, obstructive sleep apnea, asthma, and high cholesterol, all of which are among the leading causes of death among adults in the US (CDC, 2021). The direct medical cost of obesity and being overweight combined is approximately 10% of United States healthcare spending (Tsai et al., 2011). While the increased obesity is seen in all US adults, the current obesity trends are especially troubling for women. According to Healthy People 2020 (HP2020), in 2013–2016, the obesity rate of females was 11.0% higher than that of males. Notably, 10% of adult women are considered to have extreme obesity (BMI > 40), double that of men (5.5 %) (NIH, 2017). The International Agency for Research on Cancer (IARC) has identified three women-specific cancers associated with overweight and obesity, including postmenopausal breast, ovaries, and endometrial cancers (CDC,2017).

Several factors have been associated with increased obesity risk, including selenium. Selenium plays an essential role in adipocyte hypertrophy and abdominal fat accumulation (Kim et al., 2012). Selenium is an essential trace mineral element that modulates oxidative stress by regulating the production of selenoenzyme- glutathione peroxidase (Baker et al., 1993). The results of several studies conducted in the last ten years suggested that selenium is involved in thyroid hormone metabolism, reproductive health, cancer, inflammation, cardiovascular function, osteoporosis, diabetes, inflammation, and DNA synthesis (Alehagen & Aaseth, 2015; Karalis, 2019; Lewandowska et al., 2019; Sun et al., 2013; Oliva et al., 2019; Touat-Hamici et al., 2014 Wang et al., 2019). However, there is limited evidence on the direct effect of selenium level on body weight.

In addition to selenium, to date, no studies have been specifically designed to measure the impact of age, race, income, education level, and daily caloric intake on the relationship between selenium level and BMI. However, it is known that selenium levels significantly decline with age (Letsiou et al., 2014)., and obesity rates significantly differ by age group (CDC, 2020). Furthermore, obesity prevalence varies dramatically between racial, ethnic, sex, and socioeconomic groups (CDC, 2020). The prevalence of obesity in the group whose income was under the poverty threshold was the highest (42.1%) of all income groups. However, no study has explored the impact of these factors on the relationship between serum selenium and BMI.

It has been argued that the regulation of selenium metabolism is sex-specific, and the distribution of selenoproteins differs significantly between sex groups (Kim et al., 2012). In addition to selenium, there is accumulating evidence that metabolic changes in women during menopause are potentially associated with increased body weight and visceral fat accumulation (Wang et al., 2019). Postmenopausal women experience higher total body fat mass and accumulation of adiposity than premenopausal women

(Davis et al., 2012; Razmjou et al., 2018). While selenium is regarded as potent antioxidant activity (Seale et al., 2018), a recent study on postmenopausal women draws a connection between obesity and oxidative stress (Carvalho et al., 2015). Moreover, the researchers found that the dietary intake of selenium was significantly lower in obese postmenopausal women than that in lean women (Carvalho et al., 2015). In addition, animal experiments suggested that estrogen status affects tissue distribution and metabolism of selenium by modulating Sepp1, a protein that regulates selenium transport (Zhou et al., 2012). Nevertheless, the role of selenium in body weight and the impact of menopausal status in women has not been thoroughly investigated.

The purposes of this study were to investigate the following questions among US women 1) the relationship between serum selenium and BMI in US women, 2) the impact of race, age, income, education level, and daily caloric intake on the relationship between serum selenium and BMI, and 3) the role of menopause in the relationship between serum selenium and BMI.

2. Materials and methods

2.1. Study design

This study utilized the National Health and Nutrition Examination Survey (NHANES) data. NHANES is a survey cross-sectional study conducted on the non-institutionalized population of the USA using a stratified and complex, multistage probability sampling design. The present study analyzed a cohort of 2,130 women aged

≥20 years who participated in NHANES 2011-2012. The survey is designed to assess the health and nutritional status of the non-institutionalized US population via a probability cluster sample - about 5,000 participants each year. Invited participants have their data collected at homes and mobile examination centers (MECs) conducted by National Center for Health Statistics (NCHS). The NCHS Research Ethics Review Board approved the NHANES study. The NHANES information is publicly released in 2-year cycles and includes sociodemographic, dietary, physical examinations, and biomarker data. Detailed study design and data collection methodology can be found in NHAHES 2011-2012 Overview of Methodology and Data Collection Procedures (https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/overview.aspx?BeginYear=2011*).*

2.2. Participants

In the NHANES 2011–2012, racial/ethnic categories were self-reported as non-Hispanic white, non-Hispanic black, Hispanic (Mexican American and Other Hispanic), non-Hispanic Asian, and other racial—multi-racial (Other). Among 4,219 individuals aged 20 years and older who participated in the interview and medical examinations, we excluded 2,008 participants of the male sex, as well as those participants missing BMI, serum selenium, and other covariates of interest. The final sample included 2,130 women **(figure 1).**

2.3. Body Mass Index

The NHANES body measures examination was conducted in the mobile examination center (MEC) (CDC, 2017). They included weight (using a digital floor scale), height, upper leg, arm length, mid-arm circumference, waist circumference, and sagittal abdominal diameter. Examination results are saved to the study database using the Integrated Survey Information System (ISIS) anthropometry computer application. BMI values are calculated using measured height and weight values as follows: weight (kilograms)/height (meters squared) (CDC, 2017).

2.4.Serum Selenium

Whole blood specimens were collected from participants, processed, stored, and shipped to the Division of Laboratory Sciences, National Center for Environmental Health, and Centers for Disease Control and Prevention for analysis. Whole blood selenium concentrations were determined using inductively coupled plasma mass spectrometry with the lower limit of detection set at 4.5 µg/dL. This multi-element analytical technique is based on quadrupole ICP-MS technology- a highly reliable, validated, and specific method to measure the concentrations of trace minerals in blood serum utilized worldwide since 1983 **(**Tanner & Baranov, 1999; Thomas, 2003). Detailed descriptions of laboratory methodology and quality control methods for serum selenium measurements are available elsewhere from the CDC (CDC, 2017).

2.5. Other Variables

Menopausal status was assessed based on the NHANES Reproductive Health Questionnaire, where RHD042 asked participants to clarify the reason for no period in the past 12 months. Participants who answered "Menopause/Hysterectomy" were categorized as postmenopausal. The age, sex, race, income, education, and menopausal status data were derived from self-reported interview questionnaires. Daily caloric intake was determined as part of the ‘What We Eat in America’ (the dietary intake interview component of the NHANES) survey. The 24-h recall was collected using the USDA Automated Multiple-Pass instrument. We used a combination of two 24-h dietary recalls to determine a two-day mean as daily caloric intake.

2.6. Statistical analysis

Descriptive analyses were used to describe sociodemographic characteristics by measuring the means and standard deviations. The survey-weighted mean serum selenium was evaluated overall and by age group, race/ethnicity, education, and family income-to-poverty ratio. All analyses accounted for the complex survey design of NHANES. The measured variables: serum selenium and BMI, were normally distributed when checked for normality. In the second model, the relationship between SE and BMI and the impact of age group, race/ethnicity, education, and family income on the relationship between SE and BMI were assessed by multiple regression models. In the third model, the effect of menopausal status was assessed by moderated multiple regression (MMR). T-tests were performed to examine differences in serum selenium and BMI based on menopause status (premenopausal or postmenopausal). Stata version 16 (StataCorp LP, College Station, TX) was used for analysis with a significance value set top <.05.

3. Results

3.1 Characteristics of Study Population

A total of 2,130 women with a mean age of 43.8 years (SD = 14.2) were included in this study. Out of this group, 767 women (36%) self-reported at the postmenopausal stage (mean age = 58.6, SD = 7.2) and 1,363 women (64%) at the premenopausal stage (mean age = 35.7, SD = 10.2). A significantly higher portion of premenopausal women reported completing a college education or higher (32.2%) compared to postmenopausal women (21.5%). Half of the study participants reported a family monthly income of $0-USD 34,999 (49%%). The average BMI of study participants was 29.5 (SD = 7.8), 28.9 (SD = 7.8) for premenopausal women and 30.5 (SD = 7.5) for postmenopausal women. The average concentrations of serum selenium were 191.7 ug/L (SD = 27.4) in all participants, 191.0 ug/L (SD = 24.8) for premenopausal women and 193.04 ug/L (SD = 31.3), the difference was not significant ($p = 0.12$). Generally, postmenopausal women consumed fewer daily calories and had a higher mean BMI than premenopausal women ($p = 0.00$) (Table 1).

3.2 Serum Selenium and BMI

The correlations between serum selenium and BMI are present in Table 2. Based on linear regression for all women, serum selenium negatively associated with BMI (unadjusted r = -.07 , p= 0.41, 95% CI = -.23 -.10), but the association is not statistically significant (F = 0.41, R^2 = 0.0012, p= 0.41). .

3.3 The Impact of Demographics on the Relationship Between Serum Selenium and BMI. After adjusting for age, race, income, education and total calorie intake, the negative correlation between serum selenium and BMI changed from -.07 to -.04 (adjusted r = -.041, p= 0.5 , 95% CI = -.18 - .10), but was not statistically significant (F = 0.0008 R^2 = 0.10, Table 2).

3.4 The Role of Menopause in the Relationship Between Serum Selenium and BMI

The menopausal status did not significantly moderate the effect of serum selenium on BMI. Moderated multiple regression (MMR) r = -.57, p= 0.15 , 95% CI = -.24 -1.37). Model 3: Prob > F = 0.28, R^2 = 0.013 model was statistically significant. (Table 2).

4. Discussion

This study aimed to examine the relationship between serum selenium and BMI in US women and explore the role of race, age, income, education level, daily caloric intake, and menopausal status on the relationship between serum selenium and BMI. The results of our study found no statistically significant relationship between serum selenium and BMI and no statistically significant impact of age, race, income, education level, and daily caloric intake on the relationship between serum selenium and BMI. This study also found that menopause does not play a significant moderating role in the relationship between serum selenium and BMI in US women. To the best of our knowledge, this is the first study specifically designed to focus on menopausal women to examine the impact of age, race, income, education level, and daily caloric intake on the relationship between serum selenium and BMI. The most significant finding of this study was a high prevalence of overweight and obesity (68%) in all participants. Interestingly, while postmenopausal women consumed significantly fewer calories per day, they had a significantly higher prevalence of obesity compared to premenopausal women.

Our study found no significant relationship between selenium and BMI. At present, the mechanisms underlying the effect of serum selenium on BMI remain largely unclear. Current inconsistent findings in the literature included a significant inverse association between serum selenium and BMI (Zhong et al., 2018), no significant differences between obese and non-obese participants concerning selenium (Ghayour-Mobarhan et al., 2005), a significant reduction in serum selenium level among morbidly obese female patients seeking bariatric surgery (Alasfar et al., 2011) a significant quadratic relationship with BMI, being lower in individuals at the low and high ends of the BMI range (Combs et al., 2011), and the association of low serum selenium with overweight and obesity in premenopausal females (Kimmons et al., 2006). Although the current study evaluated relevant data and attempted to clarify the current state of research about the relationship between serum selenium and BMI, the findings did not produce a statistically meaningful conclusion. One possible reason for this finding is that most individuals have sufficient selenium levels. The effects of minor variations in selenium levels on BMI in this study may not be detectable. Further research should include individuals with a wide range of serum selenium and incorporate data on serum deficiency and individuals with selenium surplus. Additionally, following individuals over a long period and capturing how serum selenium levels correspond to changes in BMI will paint a better picture of the relationship between the two variables.

The results of our study found no statistically significant impact of age, race, income, education level, and daily caloric intake on the relationship between serum selenium and BMI. At this time, no studies specifically measured the impact of age, race, income, education level, and daily caloric intake on the relationship between selenium level and BMI. Considering that selenium levels significantly decline with age (Letsiou et al., 2014)., and obesity rates substantially differ by age, racial, ethnic, sex, and socioeconomic groups (CDC, 2021), it was essential to include variables that could have potentially impacted the relationship between selenium and BMI in the analysis. However, our analysis focused on women only and may have excluded groups that other important variables could have impacted. Future studies should encompass a broader range of participants to measure the impact of age, race, income, education level, and daily caloric intake on the relationship between serum selenium and BMI.

This study found that menopause does not play a significant moderating role in the relationship between serum selenium and BMI. To date, this is the first study specifically designed to focus on the relationship between serums selenium and BMI in menopausal women. Postmenopausal women experience higher total body fat mass and accumulation of adiposity than premenopausal women (Davis et al., 2012; Razmjou et al., 2018). Notably, other researchers found that the dietary intake of selenium was significantly lower in obese postmenopausal women than that in lean women (Carvalho et al., 2015). Therefore, it was important to evaluate a possible moderating effect of menopause on the relationship between serum selenium and BMI. This study only included menopause as a possible moderator between serum selenium and BMI. Future analysis should include other metabolically important factors, such as thyroid markers and physical activity levels.

Additionally, this study confirmed an alarming trend in overweight and obesity prevalence. Among 767 postmenopausal participants, 568 had a BMI >25 kg/m2, almost 75%. This trend is especially troubling because obesity during menopause puts women at a significantly high risk of cardiovascular disease and invasive breast cancer (Grygiel-Górniak et al., 2014; Neuhouser et al., 2015; Wang et al, 2021). Because overweight and obesity significantly increase the risk for medical morbidity (CDC, 2017), the assessment of risk markers for weight gain is crucial to reduce the rates of obesity. These findings are in accordance with the numerous studies which demonstrated the unfavorable effect of the menopausal transition on body composition, visceral fat deposition, and general health outcomes (Davis et al., 2012). While the issue surrounding obesity is cmplex and numerous contributing factors play a role in the worsening epidemic, several studies have indicated that certain micronutrients may be associated with increased body fat accumulation and high BMI (Wang et al., 2016). Future studies may need to identify other potential risk factors for obesity in women.

Limitations

There were several major limitations to this study. First, the cross-sectional design limits the scope to associations and does not examine causal relationships between the variables. Notably, the data analyzed the relationship between serum selenium level and BMI in healthy, non-hospitalized, selenium-sufficient adult women, limiting the findings' generalizability to numerous other groups, including those with mineral deficiencies or those with chronic or acute disorders requiring hospitalization. Furthermore, in a population with adequate selenium levels, the effects of considerably minor changes in selenium levels on body weight and composition may not be statistically noticeable or obvious. Next, although BMI is the most widely used measure of obesity, several recent studies disputed its' accuracy, validity, and specificity by comparing the results with dual-energy X-ray (gold standard). Lastly, it is possible that the analytical approach in this study may not have been sensitive enough to capture the effect of selenium on body weight.

Future Research

To date, several studies recognized the importance of selenium in thyroid function and, therefore, body metabolism. Future studies should attempt to include populations with selenium deficiency and selenium-replete participants to capture a broader range of serum levels and their effect on BMI values. Importantly, several mediating factors related to body metabolism should be considered in future analyses, including thyroid profile and physical activity level. Selenium is abundantly present in the thyroid gland and catalyzes the conversion of inactive thyroid- T4 to the active form-T3 (Duntas, 2010; Kim et al., 2012). Thyroid function and bodyweight appear to be closely correlated because the thyroid regulates basal metabolism and thermogenesis and plays an active role in lipid and glucose metabolism and fat oxidation (Longhi & Radetti, 2013). Similarly, the effect of PA on energy expenditure cannot be overlooked, and the possible mediating effect of PA on the relationship between selenium and BMI should be considered.

5. Conclusions

In a nationally representative sample of female adults in the US, no statistically significant relationship between serum selenium and BMI was observed in 2011-2012. Menopause status appears to have no statistically significant moderating effect on the relationship between selenium and BMI. Based on these results, it would be premature to conclude the association between selenium and BMI. These findings indicate the need for further clinical studies to investigate the role of selenium in body weight.

Ethical considerations

Data from NHANES were used for all analyses included in this study. The Centers for Disease Control and Prevention (CDC) Institutional Review Board and the National Center for Health Statistics (NCHS) Research Ethics Review Board approved the NHANES protocols. All participants provided written informed consent.

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Appendix C (Chapter Three Tables and Figures)

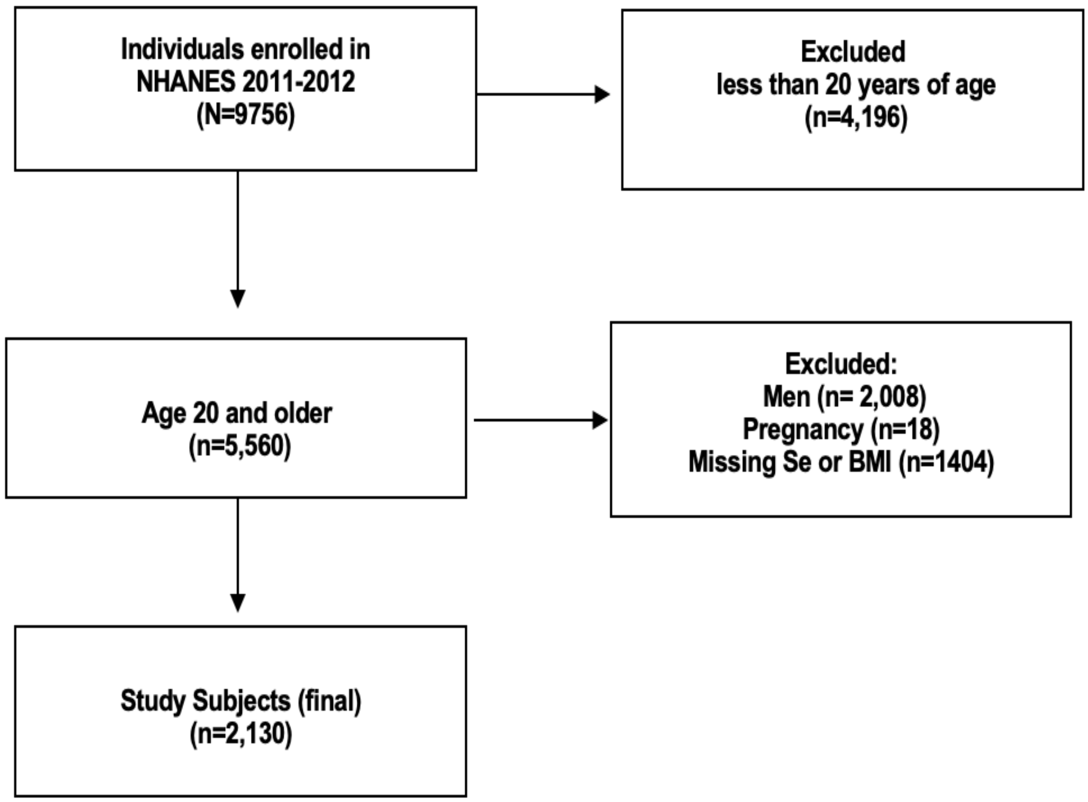

Fig. 3.1 Flow-chart of subjects' selection for analyses.

Table 3.1 Baseline characteristics of the study population by menopausal status*

Variables	All Women N=2130	Pre- Menopause N=1363	Post Menopause N=767	*p*
Age, year (Mean, SD)	43.8 (14.2)	35.7821 (10.2)	58.06 (7.2)	0.00
BMI (Mean, SD)	29.5 (7.8)	28.9 (7.8)	30.5 (7.5)	0.00
Serum selenium, ug/L (Mean, SD)	191.7 (27.4)	191.0 (24.8)	193.04 (31.3)	0.12
Race (N, %)				
Hispanic	222 (10.4)	296 (21.0)	167 (21.7)	0.00
White	698 (32.8)	449 (32.94)	249 (32.5)	0.00
Black	595 (27.9)	339 (24.8)	256 (33.4)	0.00
Asian	316 (14.8)	234 (17.2)	82 (10.7)	0.00
Other	58 (2.7)	45 (3.3)	13 (1.7)	0.00
Income (N, %)				
$0-$34,999	1,007 (49)	643 (48.8)	364 (49.3)	0.00
$35,000-$74,999	562 (27.3)	345 (26.2)	217 (29.4)	0.00
$75,000- Over	486 (23.6)	328 (24.9)	158 (21.4)	0.00
Education (N, %)				
High school or less	810 (38.0)	452 (33.2)	358 (46.7)	0.00
Some college	716 (33.6)	472 (34.6)	244 (31.8)	0.00
College Grad or above	604 (28.4)	439 (32.2)	165 (21.5)	0.00
Caloric Intake (Mean, SD)	1818.5 (671.9)	1900.58 (709.7)	1680.2 (577.7)	0.00

*Values expressed as means (SD) or percentage (SE)

Table 3.2 Linear regression analyses: serum selenium (ug/L) and BMI (kg/meters).

Variables	Coef. *r*	Std. Err. (t)	95 % CI	*p*-value
Model 1 All women N=2130 **unadjusted**	-.0669047	.0793196 (-0.84)	-.2342544, .1004451	0.411
Model 2: All women N=2130 **adjusted** [a]	-.0412577	.067674 (-0.61)	-.1840374, .1015219	0.550
Model 3: Menopause N=2130 **Moderation Effect**	.570421	.381827 (1.49)	-.2351635, 1.376006	0.154
Age	.0024652	.0005281 (4.67)	.001351, .0035795	0.00
Race				
Hispanic	.1708627	.015271 (11.19)	.1386437, .2030817	0.00
Black	.2507278	.0137495 (18.24)	.2217189, .2797366	0.00
White	.135985	.0173865 (7.82)	.0993028, .1726672	0.00
Asian	0 (omitted)	(omitted)	(omitted)	
Other Race	.0777519	.0249908 (3.11)	.0250261, .1304778	0.006
Income				
$0-$34,999	.07763	.0222623 (3.49)	.030660, .1245995	0.003
$35,000-$74,999	.0420292	.0276343 (1.52)	-.01627, .10033	0.147
$75,000- Over	.0169756	.0261499 (0.65)	-.0381958, .072147	0.525
Education				
High school or less	.0476779	.0184303 (2.59)	.0087933, .0865624-	0.019
Some college	.0432108	.0241798 (1.79)	.0078041, .0942257	0.092
College Grad or above	0 (omitted)	(omitted)	(omitted)	
Daily Caloric Intake	.000013	.0000127 (1.02)	-.000013, .000039	0.323

CHAPTER FOUR

Selenium and BMI in US Adults: An Analysis of Mediating Effects of Triiodothyronine and Physical Activity.

Abstract

The rising level of obesity is a significant public health concern. Selenium, Triiodothyronine (T3), and physical activity (PA) all play an essential role in the body's metabolism. Several studies have supported the relationship between serum selenium and weight, and yet, the role of T3 and PA in the selenium and BMI relationship has not been thoroughly explored. This study aimed to examine the role of T3 and PA in the relationship between serum selenium levels and Body Mass Index (BMI) among US adults. This study used a cross-sectional design based on the National Health and Nutrition Examination Survey (2011-2012) data. It included age, sex, race/ethnicity, income, education, daily caloric intake, BMI, and PA. Laboratory data included serum selenium and T3 levels. A total of 1,341 adult men and women were included in this study. On average, men in the study had lower BMI, higher selenium and T3 levels, higher daily caloric intake, and lower PA levels than women. In a probability sample of the US population, T3 or PA did not show a statistically significant mediating effect on the relationship between serum selenium and BMI. Adjusted for demographic factors, no statistically significant mediating effect of T3 or PA on the relationship between serum selenium and BMI among US women was found by our analysis. Further studies should include other metabolically active hormones and elements and more specific measures of physical activity (e.g., type, settings/environment) in the analysis of the connection between serum selenium, T3, PA, and obesity.

Keywords: *Selenium, BMI, Triiodothyronine (T3), Physical Activity (PA), Micronutrients, Trace Minerals*

Introduction

Across all demographic groups, obesity rates continue to rise in the United States (US) (CDC, 2021). Nearly 40% of US adults are obese, defined as body mass index (BMI) greater than 30, and 32% of adults are considered overweight, with BMI between 25 and 29.9 . Several health conditions have been linked with obesity in adults, including cardiovascular disease, high blood pressure, stroke, diabetes, obstructive sleep apnea, asthma, and high cholesterol, all of which are among the leading causes of death among adults in the US [2]. Obesity also increases health care expenses as the estimated direct cost for medical treatment for obesity and overweight is about 10% of United States healthcare spending (Tsai et al., 2011).

The etiology of obesity is complex, and several factors play a role in the global health epidemic. The role of the essential trace mineral selenium in metabolic health is currently a subject of great interest to the scientific community. Selenium is an essential element that regulates oxidative stress via the production of selenoenzyme- glutathione peroxidase (Baker et al., 1993; Touat-Hamici et al., 2014). Selenium plays a vital role in abdominal fat accumulation and adipocyte hypertrophy (Kim et al., 2012). A recent analysis of nutritional status revealed that high selenium intake is associated with a healthy weight (Wang et al., 2016). Despite multiple studies indicating that micronutrients may be associated with increased body fat accumulation and BMI (Adnan et al., 2019; Amin et al., 2020; Garcia et al., 2009; Hosseini et al., 2016) , some literature reporting on the relationship between serum selenium and weight demonstrated contradictory findings (Tinkov et al., 2020).The significant difference in findings in studies involving blood selenium levels and weight indicates the need for a more specific analysis of the relationship between selenium and BMI, including the exploration of mediating effects of metabolically active factors such as thyroid markers and physical activity.

The results of several studies conducted in the last ten years suggested that selenium is involved in thyroid hormone metabolism, reproductive health, cancer, inflammation, cardiovascular function, osteoporosis, diabetes, inflammation, and DNA synthesis (Alehagen & Aaseth, 2015; Karalis, 2019; Lewandowska et al., 2019; Sun et al., 2013; Oliva et al., 2019; Touat-Hamici et al., 2014 Wang et al., 2019). Selenium is abundantly present in the thyroid gland and catalyzes the conversion of inactive thyroid-T4 to the active form-T3 (Duntas, 2010; Kim et al., 2012). Thyroid function and bodyweight appear to be closely correlated because the thyroid regulates basal metabolism (the rate of energy expenditure per unit time at rest) and thermogenesis and plays an active role in lipid and glucose metabolism fat oxidation (Longhi & Radetti, 2013). More specifically, among overweight and obese adults with normal thyroid function, higher baseline free T3 and free T4 predicted more weight loss and maintenance, suggesting the importance of thyroid hormones in body weight regulation and metabolism (Longhi & Radetti, 2013). Triiodothyronine is the active form of the thyroid hormone thyroxine. Although the causes of thyroid problems are largely unknown, maintaining a physiological concentration of selenium has been widely recommended to prevent thyroid disease and improve immunological mechanisms in patients with autoimmune thyroiditis (ATA, 2017). Importantly, supplementation with selenium seems to have benefits in immunological mechanisms of Graves' Disease (an autoimmune process which leads to hyperthyroidism) as well as Hashimoto's Thyroiditis (an inflammatory disorder that causes hypothyroidism), both conditions are associated with bodyweight changes (Ventua et al., 2017; Wichman et al., 2016). To the authors' best knowledge, the role of T3 in the relationship between selenium and BMI has not been evaluated.

Physical activity also plays a direct role in energy expenditure and metabolism (Westerterp, 2013). The CDC recommends physical activity as one of the strategies to prevent obesity (CDC, 2017). Obesity-related research thus far suggests that diet combined with physical activity and exercise, rather than diet alone, results in significant and clinically meaningful weight loss (Curioni & Lourenco, 2005; Johns et al., 2014; Nascimento et al., 2014;). Furthermore, several recent studies found a link between physical activity and selenium concentrations in the body (Letsiou et al., 2014; Margaritis et al., 2005; Zaitseva et al., 2015). Therefore, it is crucial to consider the potential effects of physical activity when investigating the relationship between selenium and BMI.

When analyzing the mediating effect of T3 and PA on the relationship between selenium and BMI, several demographic factors like sex, race, age, income, education level, and daily caloric intake are essential to consider. Obesity prevalence varies dramatically between racial, ethnic, sex, and socioeconomic groups (CDC, 2021). The prevalence of obesity in the group whose income was under the poverty threshold was the highest (42.1%) of all income groups. According to Healthy People 2020 (HP2020), in 2013–2016, the obesity rate of females was 11.0% higher than that of males. Significantly, 10% of adult women are considered to have extreme obesity (BMI > 40), double that of men (5.5 %) (NIH, 2017). Additionally, selenium levels significantly decline with age (Letsiou et al., 2014) and obesity rates significantly differ by age groups (CDC, 2021). Adjusting for demographic factors while evaluating the mediating effect of T3 and PA on the relationship between selenium and BMI is an essential step of this study. The aim of this study is to examine the role of T3 and PA in the relationship between serum selenium levels and Body Mass Index (BMI) among US adults.

Materials and methods

The US National Health and Nutrition Examination Survey (NHANES) is a cross-sectional survey conducted on the non-institutionalized population of the USA. The study is designed to evaluate the health and nutritional status of the population with a probability cluster sample of about 5000 participants each year. The National Center for Health Statistics (NCHS), along with the Centers for Disease Control and Prevention (CDC) Institutional Review Board (IRB), reviewed and approved the NHANES protocols. All participants provided written informed consent. The NHANES information is publicly released in 2-year cycles and includes sociodemographic, physical examinations, dietary, and biomarker data. While all variables of interest were collected in multiple NHANES cycles, combined, publicly-available data on selenium, T3, PA, and BMI were only available for the NHANES 2011–2012 cycle, which is why this study limited analysis to those years.

In the NHANES 2011–2012, racial/ethnic categories were self-reported as non-Hispanic white, non-Hispanic black, Hispanic (Mexican American and Other Hispanic), non-Hispanic Asian, and other racial—multi-racial (Other). The total number of subjects aged 20-69 from all sources was 5,560**.** Participants were excluded from this study if they were missing any of the following: serum selenium, T3, BMI, or physical activity monitor data. The total number of eligible participants was 1,341 (Fig. 1). Detailed study design and data collection methodology can be found in NHAHES 2011-2012 Overview of Methodology and Data Collection Procedures (https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/overview.aspx?BeginYear=2011 *).*

Measurements

Demographics: The demographic questionnaire included age, sex, race/ethnicity, education level, and annual family income. Body Mass Index (BMI) The NHANES body measures examination was conducted in the mobile examination center (MEC). Specific measurements were completed dependent on the participant's age. They included weight (using a digital floor scale), height, upper leg, arm length, mid-arm circumference, waist circumference, and sagittal abdominal diameter. Examination results are saved to the study database using the Integrated Survey Information System (ISIS) anthropometry computer application. BMI values are calculated using measured height and weight values as follows: weight (kilograms)/height (meters squared).

Laboratory Data: Serum Selenium & Triiodothyronine (T3) Whole blood specimens were collected from participants, processed, stored, and shipped to the Division of Laboratory Sciences, National Center for Environmental Health, and Centers for Disease Control and Prevention for analysis. In the NHANES 2011–2012, serum selenium was measured in approximately one-third of adult participants. Whole blood selenium concentrations were determined using inductively coupled plasma mass spectrometry with the lower limit of detection implemented set at 4.5 μg/dL. This multi-element analytical technique is based on quadrupole ICP-MS technology- a highly reliable, validated, and specific method to measure the concentrations of trace minerals in blood serum utilized worldwide since 1983 (Tanner & Baranov, 1999; Thomas, 2003). To determine T3 levels, serum samples were analyzed for the thyroid hormones and measured using isotope dilution-high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) (CDC, 2017). Detailed descriptions of laboratory methodology and quality control methods for serum selenium measurements are available from CDC (2017).

Physical Activity: The physical activity monitor (PAM; ActiGraph model GT3X) component was reintroduced to NHANES in 2011. NHANES participants were asked to wear the PAM for seven consecutive days to collect objective information on 24-hour movement when awake and asleep. The PAM measured acceleration (i.e., on the x-, y-, and z-axes) every 1/80th of a second (80 Hz). The device also measured ambient light levels every second (1 Hz). The 80 Hz accelerometer and 1 Hz ambient light measurements were summed over each participant's minute, hour, and day. Sampling intervals at the end of the participant's MEC exam session and stop recording data eight days later (i.e., on the ninth calendar day). Activity levels were divided into three step-defined physical activity categories: sedentary (<5000 steps/day), low-to-somewhat-active (5000–9999 steps/day), and active-to-highly-active (≥10000 steps/day). The data were synthesized to produce a PA level/day variable (PAXMTSD) and used as a continuous variable in this proposed study.

Data analysis: Using Stata version 16 (StataCorp LP, College Station, TX) with a significance value set at $p < .05$, the descriptive analysis and a multilevel structural equation modeling (SEM) with adjustment for age, sex, race/ethnicity, income, education, and dietary data was applied to evaluate the mediating role of T3 and PA in the relationship between serum selenium and BMI in adult participants ≥ 20–69 years of age. The survey-weighted mean serum selenium and physical activity level were evaluated overall and by age group, race/ethnicity, education, and family income-to-poverty ratio. Summary values for continuous variables were, presented as means plus or minus standard deviations. All analyses accounted for the complex survey design of NHANES.

Results

Study Population

A total of 1,341 participants with a mean age of 43.45 years (SD = .39) were included in this study. Six hundred seventy were women (50%), and six hundred seventy-one (50%) were men out of this group. A significantly higher portion of women reported completing a college education or higher (30.2%) than men (26.5%). Half of the study participants reported a family monthly income of $0-$34,999 (48.2%). However, a significantly higher portion of men reported an income of $75,000 and over, (27%) vs. (24%) of women, respectively (p = 0.00). The average BMI of study participants was 28.9 (SD = .11), specifically for men 28.4 (SD = .13) and 29.50 (SD =.17) for women. The average concentration of serum selenium was 194.13 ug/L (SD = .42) in all participants, men had a higher average selenium level 196.55 ug/L (SD =.58) than women 191.75 ug/L (SD =.59), and the difference was significant (*p* = 0.00). Clinically relevant, the average T3 level was significantly (*p* = 0.00) higher in men 3.29 (SD=.01) than in women 3.08 (SD=.01). Furthermore, men recorded significantly lower PA levels 10616.54 steps (SD=81.51) but higher daily caloric intake 2452.53 kCal (SD=20.68) than women 11156.9 (SD=81.23) and 1818.49 (SD= 15.24), respectively (*p* = 0.00). (Table 1).

The Mediating Role of T3 on The Relationship Between Selenium And BMI

Our first unadjusted SEM model included T3 as a mediator in the relationship between selenium and BMI (Table 2). A mediation T3 on the association between selenium and BMI was not significant. (*r* = .13, *p*= 0.22 , 95% CI = -.088, .35). There were no significant direct and indirect effects from selenium to BMI in the total model (β = .03, *p* = .65) (Table 3). In model 2, after adjusting for sex, age, race, income, education, and total calorie intake, a mediation of the association between selenium and BMI through the proposed mediator T3 was not found (*r* = .13, *p*= 0.16, 95% CI = -.06, .33). The specific indirect effect of T3 (*r* =004, 95% CI = -.01, .01) was also not statistically significant (*p*=0.47), with overall model R^2 = 252 (Table 3).

The Mediating Role of PA on The Relationship Between Selenium And BMI

The unadjusted SEM model found that PA did no mediate the association between selenium and BMI. (*r* = .01, *p*= 0.86, 95% CI = -.15, .17, table 2). In model 4, after adjusting for sex, age, race, income, education, and total calorie intake, a mediation of the association between selenium and BMI through the proposed mediator PA was not statistically significant (*r* = .03, *p*= 0.71, 95% CI = -.12, .17). The specific indirect effect of PA (*r* =.01, 95% CI = -.003, .02) was also not statistically significant (*p*=0.13), with overall model R^2 = .094 (Table 3).

Discussion

This study examined the mediating effects of T3 and PA on the relationship between serum selenium and BMI in US adults. The results of our study found no statistically significant mediating effects of T3 or PA on the association between selenium and BMI when adjusting for sex, age, race, income, education level, and daily caloric intake. This study also found that men had lower BMI, higher selenium and T3 levels, higher daily caloric intake, and lower activity levels than women.

Our study found no significant mediating effect of T3 on the relationship between SE and BMI. To the best of our knowledge, no prior research has focused on evaluating the mediating role of thyroid markers on the relationship between SE and BMI in non-hospitalized adults. However, a 2015 study by (Carvalho et al., 2015) analyzed the association of selenium status with thyroid hormones and anthropometric values in dyslipidemia patients in Brazil (Carvalho et al., 2015). The researchers reported a positive association between serum selenium levels and BMI and no association between plasma selenium and thyroid hormones. Interestingly, selenium intake and T3L/T4L ratio were closely related to each other, confirming earlier findings of the potential role of selenium in converting T4 into its metabolically active form T3 (Duntas et al., 2003; Kohrle et al., 2005).

Several studies also highlighted the importance of T3 on body weight and metabolism (Liu et al., 2017; Longhi & Radetti, 2013). Specifically, the thyroid regulates basal metabolism (the rate of energy expenditure per unit time at rest) and thermogenesis and plays an active role in lipid and glucose metabolism fat oxidation (Longhi & Radetti, 2013).

Furthermore, among overweight and obese adults with normal thyroid function, higher baseline free T3 and free T4 predicted more weight loss and maintenance [40]. Based on those findings, we hypothesized that a metabolically active free T3 could mediate between serum selenium and weight, yet our results failed to demonstrate a statistically significant mediation activity. The findings may be explained by the fact that most of the study participants have a standard or optimal thyroid level of 3.19 pg/mL (SD = .01); therefore, it is unlikely to identify thyroid deficiencies or overactivity. The mediating effect of T3 on SE and BMI may be due to insufficient variations in the study sample. Future studies may want to include participants with a broader range of T3 levels to monitor changes in T3 levels and their impact on body weight over time.

Our study found no significant mediating effect of PA on the relationship between selenium and BMI. While no study has evaluated PA as a potential mediator between selenium and weight, multiple cross-sectional and interventional studies have found a link between physical activity and selenium concentrations in the body (Letsiou et al., 2014; Margaritis et al., 2005; Zaitseva et al., 2015). Because physical activity plays a vital role in metabolism due to energy expenditure, obesity-related research suggests that diet combined with physical activity and exercise, rather than diet alone, results in a significant and clinically meaningful weight loss (Curioni & Lourenco, 2005; Johns et al., 2014; Nascimento et al., 2014). Therefore, it was essential to evaluate the potential mediating effects of physical activity when investigating the relationship between selenium and BMI. One of the reasons this study did not produce statistically significant findings could be because Actigraph captured only the duration and intensity of physical activity and did not include the type and settings/environment. Future studies should evaluate the type, intensity, and settings to understand how physical activity and exercise affect the relationship between selenium and BMI.

Concerning selenium-related differences in men and women, a recent comprehensive review by Seale et al. (2018) revealed sex-dependent parameters of selenium metabolism, as well as multiple unique pathways of selenium distribution related to sex (Seale et al., 2018). Recognizing the critical physiological differences in selenium status between males and females, the authors stress the importance of considering sex differences when analyzing selenium-dependent parameters (Seale et al., 2018). Considering sex differences in T3 in our study, women are five to eight times more likely than men to have thyroid problems (ATA, 2017). Therefore, our findings can contribute to a better understanding of thyroid status differences in men and women. At present, the mechanisms underlying the effect of serum selenium on BMI remain largely unclear. In our analysis, the mediating role of T3 and PA on the relationship between selenium and BMI did not produce a statistically significant effect. Future studies may need to identify other metabolically important factors as potential mediating variables and a longitudinal design capturing changes in T3 and PA over time. Considering that selenium levels significantly decline with age (Letsiou et al., 2014) and obesity rates substantially differ by age, racial, ethnic, sex, and socioeconomic groups (CDC, 2021), the impact of demographic factors should be included in future studies. Furthermore, future studies need to explore the role of sex and metabolism on SE and BMI.

Several limitations to this study include the cross-sectional design, which limits the scope to associations and does not examine causal relationships between the variables, and the inclusion of healthy, non-hospitalized, euthyroid, selenium-sufficient adults, which limits the generalizability of the findings to numerous other groups, including those with mineral or thyroid deficiencies or those with chronic or acute disorders requiring hospitalization.

Conclusions

In a probability sample of the US population, T3 or PA did not appear to produce a statistically significant mediating effect on the relationship between serum selenium and BMI. This finding suggests the need to explore other trace minerals and hormones that could potentially affect body metabolism. Future studies may need to identify other potential mediating factors affecting selenium and weight.

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Appendix D (Chapter Four Tables and Figures)

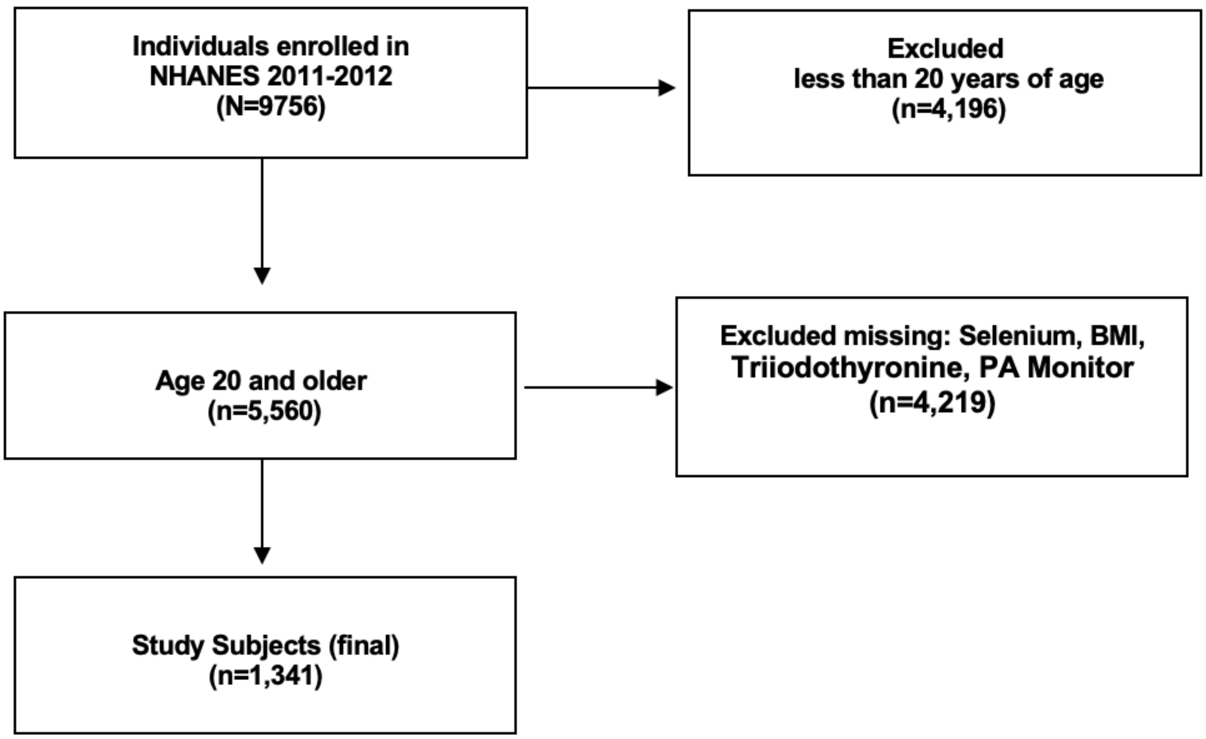

Fig. 4.1 Flow-chart of subjects' selection for analyses.

Table 4.1 Baseline characteristics of the study population

Variables	All participants N=1341	Men N=671	Women N=670	*p*
Age, year (Mean, SD)	43.45 (.39)	43.77 (.32)	43.81 (.31)	0.02
Serum selenium, ug/L (Mean, SD)	194.13 (.42)	196.55 (.58)	191.75 (.59)	0.00
Triiodothyronine (T3), pg/dL (Mean, SD)	3.19 (.01)	3.29 (.01)	3.08 (.01)	0.00
Physical Activity (Mean, SD)	10891.4 (57.70)	10616.54 (81.51)	11156.9 (81.23)	0.00
BMI (Mean, SD)	28.9 (.11)	28.4 (.13)	29.50 (.17)	0.00
Race (N, %)				
Hispanic	283 (21.10)	140 (20.86)	143 (21.34)	0.00
White	450 (33.56)	220 (32.79)	230 (34.33)	0.00
Black	353 (26.32)	178 (26.53)	175 (26.12)	0.00
Asian	216 (16.11)	113 (16.84)	103 (15.37)	0.00
Other	39 (2.91)	20 (2.98)	19 (2.84)	0.00
Income (N, %)				
$0-$34,999	616 (48.20)	309 (48.51)	307 (47.89)	0.00
$35,000-$74,999	336 (26.29)	156 (24.49)	180 (28.08)	0.00
$75,000- Over	326 (25.51)	172 (27.00)	154 (24.02)	0.00
Education (N, %)				
High school or less	535 (39.90)	289 (43.07)	246 (36.72)	0.00
Some college	426 (31.77)	204 (30.40)	222 (33.13)	0.00
College Grad or above	380 (28.34)	178 (26.53)	202 (30.15)	0.00
Caloric Intake (Mean, SD)	2134.77 (13.81)	2452.53 (20.68)	1818.49 (15.24)	0.00

Table 4.2 Multilevel Structural Equation Modeling (SEM): serum selenium (ug/L), T3 (ng/dL), PA[a], and BMI (kg/meters).

Variables N=1341	**Coef.** ***r***	**Std. Err. (t)**	**95 % CI**	***p*-value**
Model 1[b] Se (T3) BMI **unadjusted**	.1325578	.1045385 (1.27)	-.0879992, .3531	0.22
Model 2[b,c] Se (T3) BMI **adjusted**	.1334853	.0919223 (1.45)	-.0604539, .3274245	0.16
Model 3[d] Se (PA) BMI **unadjusted**	.0130666	.0758761 (0.17)	-.1470179, .1731511	0.86
Model 4[c, d] Se (PA) BMI **adjusted**	.0263108	.0695197 (0.38)	-.1203629, .1729846	0.71

[a] Mean for seven days (minutes x magnitude of acceleration)
[b] Using SEM, mediating role of T3 in Selenium ->BMI relationship
[c] Adjusted for sex, race, education, income, total daily calories
[d] Using SEM, mediating role of PA in Selenium ->BMI relationship

Table 4.3 A Summary of Total, Direct, and Indirect Effects

Effects from	**Total (95%CI)**	**Direct (95%CI)**	**Indirect (95%CI)**	***p*-value**
SE to BMI	.033 (-.117, .182)	.033 (-.117, .182)	0 (no path)	0.65
Mediating Variable: T3*	**Effect of SE on T3 (95%CI), *p*-value**	**Effect of T3 on BMI (95%CI), *p*-value**	**Specific Indirect Effect (95%CI), *p*-value**	***R^2*** **(overall model)**
	.101 (-.114, .317), 0.34	.036 (-.027, .099), 0.24	.004 (-.008, .014), 0.47	.252
Mediating Variable: PA*	**Effect of SE on PA (95%CI), *p*-value**	**Effect of PA on BMI (95%CI), *p*-value**	**Specific Indirect Effect (95%CI), *p*-value**	***R^2*** **(overall model)**
	-1026.46 (-2152.44, 99.52), 0.07	-7.85e-06 (-.00, -4.23), 0.00	.008 (-.003, .019), 0.13	.094

*Adjusted for sex, race, education, income, total daily calories

CHAPTER FIVE

Conclusion, Implications, and Future Research Recommendations

Summary of the Findings

This dissertation study aimed to investigate four important pathways related to obesity, including 1) the relationship between serum selenium and Body Mass Index (BMI) in US women, 2) the moderating role of menopause in the relationship between serum selenium and BMI, 3) the mediating role of Triiodothyronine (T3) hormone in the relationship between serum selenium levels and BMI among US adults, and 4) the mediating role of physical activity (PA) level in the relationship between serum selenium levels and BMI among US adults. Furthermore, at each step of the analysis, the impact of demographic values, including age, sex, race/ethnicity, income, education level, and daily caloric intake, was analyzed and included in the final report of the findings.

Obesity, defined by BMI, is a growing health concern. Selenium is an essential trace mineral element that plays a vital role in adipocyte hypertrophy, abdominal fat accumulation, and the conversion of inactive thyroid- T_4 to the active form-T_3 (Duntas, 2010; Kim et al., 2012). Thyroid function and physical activity are involved in energy expenditure and metabolism (Longhi & Radetti, 2013). Per CDC, 10% of adult women are considered to have extreme obesity (BMI > 40), double that of men (5.5 %) (NIH, 2017). Postmenopausal women experience higher total body fat mass and accumulation of adiposity than premenopausal women (Davis et al., 2012; Razmjou et al., 2018). However, little is known about the relationship between selenium level and BMI and the impact of menopause, T3, and PA on the relationship between selenium and body weight. This dissertation study addresses these important research gaps.

The scoping review examined the existing literature about the relationship between blood selenium levels, average physical activity level, and BMI in adults and whether the relationship was different for women compared with men. Nine studies were included in the analysis using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The studies varied in design, sample size, and findings. The scoping review found mixed results on the relationship between selenium and weight in the adult population. A wide range of conflicting findings included: a significant inverse association between serum selenium and BMI (Zhong et al., 2018), no significant differences between obese and non-obese participants concerning selenium (Ghayour-Mobarhan et al., 2005), a significant reduction in serum selenium level among morbidly obese female patients seeking bariatric surgery (Alasfar et al., 2011) a significant quadratic relationship with BMI, being lower in individuals at the low and high ends of the BMI range (Combs et al., 2011), and the association of low serum selenium with overweight and obesity in premenopausal females (Kimmons et al., 2006). While the findings varied significantly among the studies, women seemed to be at a greater risk for Selenium-related weight changes (Kimmons et al., 2006; Spina et al., 2013), which is in accordance with the theory that the hierarchical regulation of selenium metabolism under the condition of low selenium levels is sex-specific, and the distribution of melanoproteins differs significantly between sex(Letsiou et al., 2014). The scoping review made recommendations for future research based on the gaps identified in the literature. Therefore, this dissertation study examines the relationship between serum selenium level and BMI in the nationally representative sample of US adults and the role of menopause, T3, and PA in the relationship between selenium and BMI. Additionally, this study evaluates the impact of demographic factors on the variables of interest at each analysis step.

In the study evaluating the relationship between serum selenium and BMI among adult women in the US, a cohort of 2,130 women aged ≥20 years who participated in NHANES 2011-2012 were included. The moderating role of menopause was evaluated in the final step of the analysis. The results of our study found no statistically significant relationship between serum selenium and BMI and no statistically significant impact of age, race, income, education level, and daily caloric intake on the relationship between serum selenium and BMI. This study also found that menopause does not play a significant moderating role in the relationship between serum selenium and BMI. To the best of our knowledge, this is the first study specifically designed to focus on menopausal women and adjust for age, race, income, education level, and daily caloric intake on the relationship between serum selenium and BMI. The most significant finding of this study was a high prevalence of overweight and obesity (68%) in all participants. Furthermore, while postmenopausal women consumed significantly fewer calories per day, they had a significantly higher prevalence of obesity compared to premenopausal women. These findings follow the numerous studies which demonstrated the unfavorable effect of the menopausal transition on body composition, visceral fat deposition, and general health outcomes (Davis et al., 2012).

In the subsequent study, we examined the role of T3 and PA in the relationship between serum selenium levels and BMI among US adults. Furthermore, the study adjusted for sex, race, age, income, education level, and daily caloric intake on the role of T3 and PA in the selenium and BMI relationship. In a cross-sectional study design, data were collected from the NHANES 2011-2012 and included 1341 adult men and women. The results of our study found no statistically significant mediating effects of T3 or PA and no statistically significant impact of sex, age, race, income, education level, and daily caloric intake on mediating effects of T3 or PA in the relationship between serum selenium and BMI. In accordance with the evidence in the literature, this study also found that men, who represented half of the total number of participants, had lower BMI, higher selenium and T3 levels, higher daily caloric intake, and lower activity levels than women participants.

Integrating Results to the Theoretical Framework

In the introduction section of this dissertation, a theoretical framework was presented to examine the impact of menopausal status, T3, and PA on the relationship between selenium and BMI. The Homeostatic Theory of Obesity (HTO) explained the connection between selenium, BMI, demographic factors, T3, and PA. HTO proposes that imbalances explain weight gain and obesity in homeostatic processes (Marks, 2015).

The HTO explains how physiological and biochemical feedback mechanisms regulate billions of cells and thousands of reactions in the human body to maintain body temperature, blood pH, metabolism, fluid levels, blood glucose, and insulin. Furthermore, the HTO informs about the factors that could disrupt physiological and/or psychological homeostasis (or equilibrium) within the individual microsystem and contribute to obesity, including selenium level, T3 level, energy intake, expenditure (PA), and demographic components. The HTO framework allows for the integration of all variables of interest into the relationship between selenium and BMI.

Broadly, the HTO assumes that overconsumption of high-calorie, low-nutrient, and low-satiating foods, and a sedentary lifestyle combined with a challenging environment, are at the root of imbalances in homeostasis and are the ultimate cause of obesity (Marks, 2015). Postmenopausal women in our study had a significantly higher prevalence of obesity than premenopausal women while consuming significantly fewer calories per day. To assess the integrity of the homeostatic state, the impact of T3 and PA, which are both metabolically active parameters, was measured. However, results revealed that neither T3 nor PA had a statistically significant effect on the relationship between selenium and BMI. The demographic factor also did not change the significance of the connection between the variables of interest. On average, men in our study had lower BMI and higher selenium and T3 levels than women, indicating different metabolic statuses and homeostatic balance.

Significance and Implications

This dissertation has essential research and public health implications. While several previous studies have supported the relationship between serum selenium and weight (Alasfar et al., 2011; Combs et al., 2011; Kimmons et al., 2006; Zhong et al., 2018), the role of menopausal status, T3, and PA in the selenium and BMI relationship has not been thoroughly explored. Obesity remains a significant health concern, and every possible causal factor needs to be investigated. Analyzing menopausal status, T3, and PA in the relationship between selenium and BMI helps address the gaps in the literature and guides further research. Scientists can consider the findings of this study while exploring possible factors associated with obesity.

Finally, the findings of this dissertation can also guide public health interventions. The study revealed that men had lower BMI and higher selenium and T3 levels among US adults, and postmenopausal women had a significantly higher prevalence of obesity than premenopausal women while consuming significantly fewer calories per day. Women, especially menopausal women, are in a significant risk group, indicating the need to promote obesity intervention services for this vulnerable population.

Recommendations for Future Research

Currently, the mechanisms underlying the effect of serum selenium on BMI remain largely unclear. After controlling for age, income, race, education level, and daily caloric intake, the analysis of the moderating role of the menopausal status and the mediating role of T3 and PA on the relationship between selenium and BMI, the analysis did not produce statistically significant results. However, several clinically important factors were identified. In analyzing a nationally representative sample of US adults, men had lower BMI and higher selenium and T3 levels. Furthermore, while postmenopausal women consumed significantly fewer calories per day, they had a significantly higher prevalence of obesity compared to premenopausal women. Future studies need to explore the role of sex on SE and BMI. Furthermore, future studies need to identify and evaluate other metabolically important factors as potential mediating variables and employ a longitudinal design capturing changes in T3 and PA over time. Finally, future analysis studies should include populations with selenium deficiency and selenium-replete participants to capture a broader range of serum levels and their effect on BMI values.

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