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SHIFT WORK, SLEEP, AND THYROID FUNCTION IN THE NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (2007-2012)

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Abstract

Background

Night shift work and poor sleep quality are associated with a wide range of chronic diseases, including thyroid disease. Several of studies have evaluated an association between night shift work and thyroid hormones but fewer studies have evaluated an association between thyroid function and poor sleep quality or sleep duration. To examine possible links, this study examines night shift work, sleep duration and sleep quality and their association to five thyroid biomarkers: thyroid stimulating hormone (TSH) triiodothyronine (free T3 and total T3), thyroxine (free T4and total T4), thyroid peroxidase antibodies (TPO) and antithyroglobulin antibodies (ATG).

Methods

Data from the National Health and Nutrition Examination Survey (NHANES) from 2007 to 2012 was obtained from the Center for Disease Control and Prevention (CDC) website. Three cycles were combined to increase sample size. The relationship between night shift work and biomarker levels was analyzed using general linear regression models adjusted for a) age, b) ethnicity, gender and alcohol consumption. In addition, the association of sleep duration and quality and thyroid biomarkers was evaluated in age and multi-variable adjusted models and beta coefficients and 95% CI were reported.

Results

The analytic sample comprised 4,095 participants from the United States. The main results show that evening workers have increased TSH ($p<0.05$) and ATG ($p<0.05$) and T3 ($p<0.05$) levels compared to daytime workers. However, no difference in the examined biomarkers was found between night shift and day workers ($p>0.05$). Thyroid levels did not show any significant difference ($p>0.05$) across sleep duration categories (<6 hours, 7 hours, >8 hours). Participants suffering from sleep problems experience decreased T3 (free and total) levels ($p<0.05$).

Conclusion

Overall, night shift work or sleep duration was not associated with altered thyroid biomarker levels. However, evening workers were at risk of higher thyroid biomarker levels, compared to day workers, and people with sleep problems had lower T3 levels than people who do not have sleep problems.

Keywords: night shift work; thyroid biomarkers; thyroid hormones; sleep problems; sleep duration

I. Introduction

1.1. The thyroid gland

The thyroid is a small gland that secretes hormones and is found at the bottom of the neck. It is essential for one's health to have a normal thyroid hormone status [1]. In fact, thyroid hormones are as important for regular physical and intellectual development, as well as growth, in infancy and childhood as they are in adult life for protein synthesis, oxygen consumption, heat generation, and overall metabolic activity [1].

1.1.1. Thyroid hormones

Thyroid hormones consist of thyroxine and triiodothyronine. Thyroxine carries 4 atoms of iodine and is also referred to as T4, and triiodothyronine carries 3 atoms of iodine and is also referred to as T3 [1,2]. The main thyroid production is T4, however, it is transformed to T3, which is a more active form of hormone [1]. Furthermore, T3 and T4 can be either circulating freely, or they can be bound to a transport protein [2].

Normal levels of thyroid hormones are maintained through the hypothalamic-pituitary-thyroid (HPT) axis [1]. The central regulator of the HPT axis is the thyrotropin-releasing hormone (TRH), which is transported to the pituitary gland through the hypothalamus-hypophyseal portal and stimulates the synthesis and secretion of thyroid stimulating hormone (TSH) by the anterior pituitary gland [1,3]. TSH allows T4 release, which is subsequently converted into T3 in peripheral tissues. T4 and T3 exert a negative feedback effect at the hypothalamic and pituitary levels, which permits the maintaining of constant thyroid hormone blood levels [1].

Thyroid hormones are catalyzed by a protein called thyroglobulin (Tg). In fact, T4 is produced through two steps: iodination of the tyrosines of Tg and the coupling of two doubly iodinated tyrosines within Tg [4]. Synthesis is based on iodide availability. Thus, appropriate iodide consumption is required continuously throughout human life [4,5]. Tg is found in high concentrations in the colloid of the thyroid and serum of most normal people. The production and synthesis happen in the thyroid gland and the secretion by the follicular cells

takes place in the colloid of the thyroid gland. Elevated blood concentrations of Tg may be observed in benign
conditions such as thyroiditis or hyperthyroidism and in malignant conditions such as follicular thyroid carcinoma [6].

Another protein involved in thyroid hormone biosynthesis is thyroid peroxidase (TPO), which is located in the membrane of thyroid cells [7,8]. In addition to being an enzyme, it is also an autoantigen in autoimmune thyroid disease that plays a significant role in the destruction of the thyroid gland through autoantibodies (TPOAb) [7,8]. Patients suffering from autoimmune thyroid diseases develop autoantibodies against thyroid peroxidase (TPO) and also usually against thyroglobulin. [7].

1.1.2. Thyroid disease prevalence

According to the Thyroid Association of America [9], "more than 12% of the American population will develop a thyroid condition during their lifetime". Approximately 20 million Americans currently suffer from some form of thyroid dysfunction and, in addition, as many as 60% of individuals with thyroid disorder are not aware of their condition and might put themselves at risk of critical diseases including cardiovascular disease, osteoporosis and infertility, if not diagnosed and treated [9].

1.1.3. Thyroid disease types

Thyroid diseases range from minor structural changes that will have no impact on the patient's lifestyle to severe diseases that may lessen their quality of life [10]. The strongest risk factor for thyroid diseases is inappropriate iodine intake [10]. According to Vanderpump et al. [11], "almost one third of the world's population lives in regions of iodine deficiency" (p40).

1.1.3.1. Goiter and thyroid nodules

According to Carlé et al. [10], "more than one tenth of the world population is to some degree affected by goiter and most of these harbor nodules" (p465). Approximately 80% of the

people living in regions of extreme iodine deficiency are affected by goiter [11]. In fact, diffuse goiter is the most common thyroid disease. Its prevalence generally decreases with age and is greatest in premenopausal women. Furthermore, women are at least four times more affected than men [11] Iodization programs have been shown to be effective at reducing the size of goiter and preventing its growth [11]. This seems contrary to the higher number of antibodies found in older people or the increase of nodule frequency [11].

1.1.3.2. Thyroid cancer

"Thyroid cancer is the fifth most common cancer in women in the USA", according to Cabanillas et al. [12] (p2783). Due to an expansion of screening and surveillance, thyroid cancer's incidence has risen worldwide. However, mortality has remained almost unchanged over the last fifty years. Thyroid cancers can range from indolent tumors associated with low mortality, in most cases, to more aggressive forms of cancer such as anaplastic thyroid cancer [11,12].

1.1.3.3. Autoimmune thyroiditis

According to early post-mortem studies, 27% of women and 5% of men present asymptomatic autoimmune thyroiditis [11]. Predominantly, children and adolescents suffering from acquired hypothyroidism or people suffering from nonendemic goiter find the cause of their disease in autoimmune thyroiditis. The term 'thyroiditis' refers to an inflammation of the thyroid gland, and patients affected by it have more elevated autoimmune thyroid antibodies (TgAb and TPOAb) [13].

1.1.3.4. Hypothyroidism

Studies have shown that hypothyroidism and subclinical hypothyroidism affect about 10% of the global population. It is characterized by excessive TSH levels due to low levels of thyroid hormones, and thus, subclinical hypothyroidism is diagnosed with high TSH levels [11,14]. Given the lower hormone levels, the body's processes begin slowing down, therefore some symptoms consist of lower tolerance to cold, drier skin, tiredness, or depression. Hashimoto's thyroiditis is one of the most frequent causes of hypothyroidism [15].

1.1.3.5. Hyperthyroidism

According to Reddy et al. [16], "The prevalence of hyperthyroidism in the United States is approximately 1.2% (0.5% overt and 0.7% subclinical)" (p.546). An overactive thyroid gland can lead to excessive release of thyroid hormones and hyperthyroidism occurs. [16]. Subclinical hyperthyroidism is characterized by undetectable TSH blood levels but normal free T4 and T3 levels, whereas overt hyperthyroidism is characterized by undetectable TSH levels but elevated T3 and/or free T4 levels [16]. Given the excessive levels of thyroid hormones every body function has a tendency to speed up, therefore a number of symptoms are nervousness, increased sweating, or anxiety. Graves' disease is the most common form of hyperthyroidism [17].

1.1.4. Risk factors

Some factors can increase the risk of developing thyroid-related diseases:

- age: the prevalence of hypothyroidism increases with age [18].
- smoking: smokers or ex-smokers present a higher risk of developing hyperthyroidism than non-smokers [19].
- iodine consumption: a low iodine diet or a rich iodine diet may increase the risk of thyroid-related diseases (hypothyroidism), as iodine catalyzes T3 and T4 synthesis [11].
- a family history of thyroid disorders: this increases the risk of suffering from thyroid-related diseases, especially differentiated thyroid cancer [20].
- medication: some medications may increase the risk of developing thyroid disorders, such as autoimmune thyroiditis or hypothyroidism, due to iodides in preparations [21].
- gender: women are more at risk of developing thyroid disorders, especially subclinical hypothyroidism in addition to thyroid autoimmunity [22].

1.2. Night shift work and thyroid function

It is widely recognized that night shift work has damaging effects on health, such as an increased risk of cardiovascular disease and cancer [23]. Night shift work, according to the

International Labor Organization, is defined as “all work which is performed during a period of no less than seven consecutive hours, including the interval from midnight to 5 a.m.”. [24].

Working on night shifts interferes with the sleep/wake cycle and the circadian rhythm. This leads to circadian and sleep disruption, and eventually, to a negative impact on health [23]. Experimental and observational studies show that night workers, due to being exposed to light during the night, have disturbed levels of melatonin, sex steroid hormones, growth hormone, or cortisol…etc. [25,26]. Therefore, sleep and the circadian system play an important role in the endocrine system [27].

Regular sleep conditions are characterized by TSH levels exhibiting a daily rhythm: in the early evening before sleep, TSH plasma concentration begins to rise, reaching a peak at the beginning of the night [27,28]. By the end of the sleeping period, plasma levels will have decreased to attain low levels during the day. Thus, when people work in night shifts, TSH secretion continues to rise during their sleep deprivation instead of decreasing, resulting in higher plasma levels of the hormone in the morning, compared to individuals with regular sleep. [27,28].

Several studies have evaluated the association between night shift work and thyroid disease, or the relationship between TSH levels and night work [2]. A Systematic Review [28] suggested an association between higher TSH levels and night shift work. A study conducted by Moon et al. [23] suggests that night shift workers have higher TSH levels than day-shift workers, which can increase the risk of subclinical hyperthyroidism. The risk rises with the years of employment as a night shift worker [23]. A prospective study among postmenopausal women showed that those with higher insomnia scores had a significantly higher risk of thyroid cancer [23].

An additional study conducted by Hollowell and al. [29] suggested that thyroid biomarker profiles may change depending on ethnicity: antithyroid antibodies are shown to be higher in whites and Mexican-Americans than in blacks [29].

Evaluating a potential link between shift work and thyroid disease seems to be a rather interesting health topic given the prevalence of night workers, estimated to be one fifth of workers, as well as the prevalence of individuals affected by thyroid diseases, estimated at 750 million [28]. This present study evaluates the association between shift work and thyroid disease based on the biomarkers of thyroid function in the NHANES database.

1.3. Sleep and thyroid function

Sleep-related disturbances have a significant impact on health [30]. Hormone secretion is regulated by sleep and the circadian system, notably through the sympathetic nervous system and signals [31]. Thus, poor sleep quality or short sleep duration can affect the body's ability to regulate, control and produce thyroid hormones [31]. A study on the HPT axis and sleep found that "Short-term sleep restriction significantly reduces the amplitude of nocturnal TSH secretion and may modulate active thyroid hormone secretion, likely through an increased sympathetic tone". This study also shows that TSH can modulate the sleep quality. In fact, normal sleep can be observed when TSH levels are low whereas high TSH levels can lower sleep quantity and quality. [32]. Another study showed that disruption of the circadian rhythm and poor sleep quality can enhance risk for thyroid disorders like thyroid nodules [33].

1.4. National Health and Nutrition Survey (NHANES)

The National Health and Nutrition Examination Survey (NHANES) evaluates the health and dietary status of children and adults in the United States of America [34]. It is a major program of the National Center for Health Statistics (NCHS) that is itself a part of the Centers for Disease Control and Prevention (CDC). The NHANES program started in the early 1960s and since 1999 it has consisted of a number of health and nutrition measures which meet emerging needs, in addition to providing essential health statistics for the nation. The survey combines interviews and physical examinations each year on a nationally representative sample of approximately 5,000 people [34].

The NHANES interview consists of demographic, socioeconomic, dietary, and health questions, and the examination component includes medical, dental, and physiological

measures, in addition to laboratory tests administered by particularly certified medical personnel [34]. These results are then used to determine prevalence and risk factors for diseases [34]. The outcomes also serve as the premise for national standards for measures including height, weight and blood pressure. Another use of the survey records is the exploitation of the data for epidemiologic studies and health research, which permits the development of public health policy, the layout of health programs, and the expansion of health knowledge [34].

II. Aim / Study objectives / Hypotheses

2.1. Aim

The research question is: "How does night shift work and sleep influence thyroid biomarker levels in the National Health and Nutrition Examination Survey (NHANES) between 2007 and 2012 ?

2.2. Study objectives

Main Aim

To examine the association between night shift work, sleep and some selected biomarkers of thyroid function, in the NHANES study in three cycles: from 2007 to 2008, from 2009 to 2010, and from 2011 to 2012.

Secondary aims

- Examination of the potential change in effects by gender (males, females): previous studies suggest that women working nights or rotating shifts are at higher risk of adverse health effects [35]. This study aims to establish whether women on night shift work experience a higher risk of thyroid problems.
- Examination of the change in effects by ethnicity (non-Hispanic whites, non-Hispanic blacks and Mexican-Americans). Studies suggest that, in the USA, there is a high prevalence of African-Americans working night shifts, and that they have an increased risk of health effects [36]. This analysis aims to establish which ethnicity is more at risk of thyroid problems when working night shifts.

- Examination of the change in effects by sleep (sleep duration and self-reported sleep problems). This analysis aims to establish whether people with poor sleep quality are at higher risk of suffering from thyroid diseases when working night shifts.
- Examination of the association of clinically significant biomarker levels and work schedule.

2.3. Hypotheses

We hypothesized that night shift work schedules are associated with more unfavorable biomarker profiles related to thyroid disease and autoimmunity when compared to normal daytime hour schedules. We also hypothesized that night shift workers with sleep problems or short sleep (defined as low shift work tolerance) have worse biomarker profiles compared to night shift workers without sleep problems. Additionally, we hypothesized that the effect of night shift work on thyroid levels would be modified by gender, race/ethnicity, sleep duration and sleep problems.

III. Methods

3.1. Study type and design

The study design is a cross-sectional study. Current night shift work status (regular daytime schedule, regular evening shift, regular night shift, rotating shifts, another), an independent qualitative variable, is also assessed at a given time in individuals from three consecutive NHANES data cycles: 2007-2008, 2009-2010 and 2011-2012.

3.2. Study population and settings

The studied population is the NHANES population in three cycles, from 2007 to 2008, from 2009 to 2010, and from 2011 to 2012. These cycles were chosen because they are the only

ones for which the outcome (thyroid biomarkers) and the exposure information are available.

Inclusion Criteria :

All survey participants aged 16 years and older were eligible.

Exclusion criteria :

- Participants with missing information on biomarkers and shift work status
- Pregnant women

3.3. Sampling method

After a four-stage sample design, the total non-institutionalized U.S. civilian population residing in the 50 States of America is represented in the NHANES sample [37]. The first sample step allows the selection of the primary sample units, which are U.S. counties [37]. The second step consists of the selection of area segments, where every primary sample unit is designed to produce an equal sample size [37]. The third step consists of dwelling units. A subsample of these units is designated to identifying potential participating households. Each household in the subsample has an approximately equal probability of being included in the national sample [37]. People living in households make up the fourth stage of sample selection. A subsample of persons is chosen based on gender, age, ethnicity and income from all eligible members of a household, using a screening procedure run by interviewers, who visit each sample household [37].

The NHANES data provides design weights, which account for the survey design, like oversampling, nonresponse and post-stratification adjustments [38]. Weights translate to the number of individuals in the population that each sampled individual represents [38]. Thus, every person from the NHANES data has a sample weight assigned [39]. Sample weights are designed to reduce nonresponse bias when there are differences between the characteristics of respondents and non-respondents. According to J. Friedman, “they also account for smaller subgroups in the population by reconfiguring the sample and yielding accurate population estimates” [40].

3.4. Studied parameters and data collection

The biomarkers to be analyzed are the following:

Hormones

- Thyroid stimulating hormone (TSH) (µlU/mL) Thyroxine (T4), free (ng/dL)
- Triiodothyronine (T3), free (pg/mL)
- Thyroxine, total (T4) (ug/dL)
- Triiodothyronine (T3), total (ng/dL)

Antibodies

- Thyroid peroxidase antibodies (IU/mL)
- Thyroglobulin antibodies (IU/mL)

Shift work and sleep information

Work schedule parameters included daytime schedule, evening schedule, night shift schedule, rotating schedule and other schedule.

Sleep parameters included self-reported sleeping problems, diagnosed sleep disorders and average length of sleep per night (hours).

Information on confounders

In order to select the final confounders included in the analysis, a directed acyclic graph (DAG) was constructed, using daggity online. A DAG is a graph that shows the causal relationships between variables. The variables added to the graph were the following : age, gender, race/ethnicity, iodine levels (µg/L), marital status, education, family income to poverty ratio, physical activity, alcohol consumption, body mass index (continuous), smoking/non-smoking, the average length of sleep, hours worked the previous week, self-reported history of thyroid disease (yes/no), current thyroid disease, and intake of medications. If one of these is a predecessor of both the exposure and the outcome, they were analyzed as confounders. Result of the DAG (See Appendix 12.5.) suggested adjusting for age, ethnicity, gender and alcohol consumption.

3.5. Organization and data collection

3.5.1. Questionnaires

Interviews were conducted in participants' homes with a Household Interview or in Mobile Examination Centers (MEC). Information was recorded with computerized questionnaires, and once the data collection was over, the files were transmitted to a central survey database system [41].

The Household Interview component comprises different questionnaires. The first one is a screening questionnaire to determine whether any resident is eligible, by collecting demographic characteristics. Then, the participant is asked medical history questions, he is also asked to answer a family interview questionnaire, and lastly, he is asked to answer the sample person questionnaire, which comprises all sorts of medical and non-medical questions. After this, participants are asked to schedule an appointment at the MEC [41].

The MEC Interview has two interview parts and both of them address health-associated topics. The personal interview is carried out in a private room by a trained interviewer. The Audio Computerized Self-Administered (A-CASI) part is carried out in a private room within the MEC, where the respondents are alone and can progress throughout the questionnaire at their own pace. The A-CASI includes five separate sections, each of which offers a sensitive health risk behavior topic [41].

Given the large prevalence of Spanish speakers living in the USA, every questionnaire is translated into Spanish by native Spanish speakers, and a large percentage of interviewers are bilingual English/Spanish [41].

3.5.2. Laboratory data

Laboratory data used specifically in our study, which consists of health measurements, was collected in MECs and specific laboratories [42]. The data was then recorded directly into the database. Every blood and pregnancy analysis was done in MECs, while other analyses were carried out in laboratories across the United States [42]. All analyses were performed by

trained staff with a degree in medical technology. A Laboratory/Medical Technologist Procedure Manual specifies how each procedure, method and process is to be conducted [42].

Guidelines are provided by the NCHS and contractors with standards for naming variable or handling missing values. Contractors were hired to perform consistency checks between interrelated variables as well as to verify extremely high and low values. Results lower than the detection limit were replaced with a value ($\frac{detection\ limit}{\sqrt{2}}$) to help distinguish undetectable results from measured results [42].

All thyroid biomarkers were collected using immuno-enzymatic assays, and a calibration curve was used to calculate thyroid biomarker concentrations. These calibrators are standardized using World Health Organization (WHO) international standards, and the curve was calibrated every given day (depending on the specific thyroid biomarker), or every time reagents with new lot numbers were used. In addition, control tests were run for each test series. A test series was invalidated if the control test did not conform to specifications defined by the quality control manual [43].

3.6. Data processing and statistical analysis plan

The statistical analysis of the data was conducted with the use of R studio. In a first step, the three surveys (2007-2008, 2009-2010 and 2011-2012) were combined using a merge and a bind command, to increase the sample size and improve statistical power.

Usually, if NHANES study findings are destined to be extrapolated to the national population, all analyses must include the primary sampling unit variable, the stratum variable, and the weighting variable for all cycles. This allows to adjust for the survey design and oversampling in some populations [44]. However, this study will not extrapolate results to the national population, so these variables were not included in the analyses.

Descriptive statistics including proportions and means were used to describe the characteristics of the study sample. P-Values were obtained using an X2 test for every qualitative variable, and ANOVA or Kruskall Wallis for every quantitative variable.

The distribution of the biomarkers was assessed to check normality using histograms. If the distribution of a thyroid biomarker was skewed, it was log-transformed to approximate normal distribution in order to increase the validity of statistical analysis [45]. Log transformation permits the outspreading of groups of data and brings together stretched out data. That implies that if some data has to be transformed, the beta coefficient and IC95% are not analyzed as any other continuous variable. They must be transformed for analysis as follows: (exp(beta coefficient) – 1) * 100. This gives the percentage increase or decrease in the outcome [46].

General linear models (GLMs) were used to compare mean levels of thyroid biomarkers in regular day-shift workers (reference group) to night shift workers, regular day-shift workers, regular evening-shift workers, and other schedule workers. The thyroid biomarkers among the different groups were further analyzed with adjustment for age in a first step, then multi-variable adjusted for confounders: age, gender, race/ethnicity, and alcohol consumption. Lastly, the thyroid biomarkers were analyzed in a mutually adjusted model with sleep duration, self-reported sleep problems and diagnosed sleep disorders.

GLMs were then used to compare mean levels of thyroid biomarkers among short sleepers, long sleepers and normal sleepers, as well as those with sleep problems. As with work schedule, there were age-adjusted, multi-variable adjusted and mutually adjusted with shift work models.

To test effect modification, stratified analyses were performed in strata of gender, ethnicity and sleep.

Multi-variable logistic regression was used to evaluate the association between shift work and clinically significant levels of thyroid biomarkers (below or above reference ranges). NHANES recommended cut-off values were used to define normal and abnormal values of TSH, free T3 (fT3), free T4 (fT4), and thyroid antibodies:

- Abnormally low TSH was defined as a TSH <0.34 µIU /mL
- High TSH as a TSH >5.6 µIU/mL
- A low fT3 as low as <2.5 pg/mL
- A low fT4 as low as < 0.6 ng/dL
- Antibody positivity was defined as TPOAb >9.0 IU/mL and TgAb >4.0 IU/mL.

3.7. Quality control (quantitative approach) or Quality criteria (qualitative approach)

3.7.1. Quality criteria

To ensure that high-quality data were gathered throughout the survey, the National Center for Health Statistics (NCHS) has numerous types of quality control monitoring methods, for instance, interviewer monitoring [41]. All interviewers complete a two-week training program and are regularly accompanied on interviews and observed to check that the interviews are conducted correctly [41].

Another quality control approach is a data collection check. The computer-administered personal interview has integrated consistency and edit checks to lessen data entry errors. Interviewers are alerted whenever uncommon responses are recorded so that they can be verified [40]. Variable frequency counts are evaluated throughout data preparation, as is the plausibility of answers to the questions [41].

Moreover, every component's survey codebook contains "check item" variables, which are used by the NCHS as part of a quality control procedure to ensure that the data collection process is correct [40].

3.7.2. Quality control

To ensure a high quality of work, the laboratory staff are observed during unscheduled visits where consultants examine them and give them feedback. Moreover, retraining sessions are planned every year to make sure the staff still possess the required skills [42].

To monitor the analysis quality, NCHS has developed a quality control protocol for each laboratory working for NHANES. NCHS also provides guidelines to standardize data processing and has developed data editing specifications to verify variable consistencies [42].

IV. Research team

The team involved in this study of the NHANES data consists of:

- **Kyriaki Papantoniou** (promoter), PhD, Associate Professor of Epidemiology, Medical University of Vienna, Public Health Center, Department of Epidemiology, Vienna, Austria.
- **Lin Yang** (co-promoter), PhD, Research Scientist/Epidemiologist, Department of Cancer Epidemiology and Prevention Research, Cancer Care Alberta, Alberta Health Services, Canada.
- **Sebastian Hödlmoser**, PhD candidate in Epidemiology, Medical University of Vienna, Department of Epidemiology, Vienna, Austria.
- **Kira Damas**, Public Health Master student, majoring in Epidemiology and Health Economics, University of Liège, Belgium.

V. Study sponsors and source of funding

No funding was obtained for this analysis.

VI. Regulatory aspects

6.1. Ethics Committee

The NHANES Research Ethics Review Board approved the protocol for the three NHANES cycles and consent was obtained from every participant [47]. Since the NHANES data is public there is no need for further ethics approval.

6.2. Privacy and data protection/Information and consent

The National Center for Health Statistics (NCHS) and the NHANES programs are committed to protecting the participants' privacy. No personal data can be released without the consent of the individuals and all data relating to or describing identifiable traits of individuals can

only be used for statistical purposes. NCHS staff, contractors, and agents are not allowed to divulge responses in identifiable form without the consent of the individual, as stated by the NHANES [47], “according to section 308(d) of the Public Health Service Act (42 U.S.C. 242m(d)) and the Confidential Information Protection and Statistical Efficiency Act of 2002 (CIPSEA, Title 5 of Public Law 107-347)” [48].

Anyone operating on NHANES must sign a pledge and follow special rules for dealing with private information. These guidelines are intended to ensure that the privacy of the people taking part in the NHANES is completely respected. Family names, addresses, smartphone numbers, locations of work are removed. Data are not launched if they are for a geographical place so small that the numbers might identify someone. Furthermore, computer systems are password protected and data are encrypted for added security [49].

Additionally, NCHS follows the “Federal Cybersecurity Enhancement Act of 2015” [48]. Federal authorities are required by law to use computer security programs to prevent cyber security risks such as hacking, internet attacks, and other security flaws in federal computer networks. In order to protect information sent, stored on, or processed by government networks, the Act allows software programs to scan it. Furthermore, computer network professionals working for the government may examine the information system for specific dangers, if a cyber-security issue is found [49]. This means the NHANES dataset has been completely anonymized before uploading the data on the website.

6.3. Insurance

A classic "civil liability" insurance covers students of the Public Health Master from the University of Liège.

VII. Results and publication

This research was carried out within the framework of a dissertation. The results will potentially be published in scientific journals.

VIII. Results

8.1. Descriptive analyses

Table 1. Qualitative characteristics of study participants according to work schedule

Baseline Characteristics		**Daytime**	**Evening**	**Night**	**Rotating**	**Another**	
		N(%)	*N(%)*	*N(%)*	*N(%)*	*N(%)*	p-value
Gender	Male	1600 (54.0%)	143 (53.2%)	111 (58.4%)	172 (47.6%)	172 (55.3%)	0.11
	Female	1364 (46.0%)	126 (46.8%)	79 (41.6%)	189 (52.4%)	139 (44.7%)	
Ethnicity	Mexican-American	631 (21.3%)	42 (15.6%)	38 (20.0%)	81 (22.4%)	37 (11.9%)	<0.001
	Black	472 (15.9%)	64 (23.8%)	55 (28.9%)	85 (23.5%)	62 (19.9%)	
	White	1330 (44.9%)	114 (42.4%)	64 (33.7%)	138 (38.2%)	172 (55.3%)	
	Other Hispanic	376 (12.7%)	33 (12.3%)	26 (13.7%)	44 (12.2%)	25 (8.0%)	
	Other Ethnicity	155 (5.2%)	16 (5.9%)	7 (3.7%)	13 (3.6%)	15 (4.8%)	
Education	Less than 9th Grade	261 (8.8%)	19 (7.1%)	23 (12.1%)	28 (7.8%)	13 (4.2%)	<0.001
	9-12th Grade	466 (15.7%)	71 (26.4%)	38 (20.0%)	79 (21.9%)	58 (18.6%)	
	High School Graduate	678 (22.9%)	77 (28.6%)	60 (31.6%)	96 (26.6%)	59 (19.0%)	
	AA, College or above	1558 (52.6%)	102 (37.9%)	69 (36.3%)	158 (43.8%)	181 (58.2%)	
Marital Status	Divorced	300 (10.5%)	21 (10.3%)	13 (7.6%)	35 (11.6%)	37 (12.8%)	<0.001
	Living with partner	250 (8.7%)	26 (12.7%)	14 (8.2%)	27 (8.9%)	21 (7.3%)	
	Married	1701 (59.4%)	81 (39.7%)	83 (48.8%)	127 (41.9%)	153 (53.1%)	
	Never married	449 (15.7%)	58 (28.4%)	47 (27.6%)	98 (32.3%)	53 (18.4%)	
	Separated	101 (3.5%)	13 (6.4%)	11 (6.5%)	9 (3.0%)	11 (3.8%)	
	Widowed	63 (2.2%)	5 (2.5%)	2 (1.2%)	7 (2.3%)	13 (4.5%)	
Self-reported sleep problems	No	2437 (82.3%)	231 (85.9%)	155 (82.0%)	294 (81.4%)	230 (74.0%)	0.003
	Yes	525 (17.7%)	38 (14.1%)	34 (18.0%)	67 (18.6%)	81 (26.0%)	

Diagnosed sleep disorder	No	2788 (94.3%)	258 (95.9%)	178 (94.2%)	345 (95.6%)	284 (91.6%)	0.16
	Yes	168 (5.7%)	11 (4.1%)	11 (5.8%)	16 (4.4%)	26 (8.4%)	
Alcohol consumption	Heavy drinker	906 (38.1%)	60 (38.0%)	45 (33.8%)	99 (39.4%)	94 (39.0%)	0.86
	Non/moderate drinker	1472 (61.9%)	98 (62.0%)	88 (66.2%)	152 (60.6%)	147 (61.0%)	
Physical activity	Low	1449 (48.9%)	139 (51.7%)	108 (56.8%)	170 (47.2%)	135 (43.4%)	0.09
	Intermediate	61 (2.1%)	6 (2.2%)	2 (1.1%)	11 (3.1%)	4 (1.3%)	
	High	1454 (49.1%)	124 (46.1%)	80 (42.1%)	179 (49.7%)	172 (55.3%)	
Smoking	Current smoker	607 (21.2%)	61 (29.9%)	54 (31.8%)	71 (23.5%)	65 (22.6%)	0.001
	Never smoker	1639 (57.3%)	101 (49.5%)	90 (52.9%)	182 (60.3%)	153 (53.1%)	
	Past smoker	616 (21.5%)	42 (20.6%)	26 (15.3%)	49 (16.2%)	70 (24.3%)	
Ever had thyroid disorder	No	2665 (93.2%)	187 (91.7%)	160 (94.1%)	284 (94.4%)	258 (89.6%)	0.13
	Yes	194 (6.8%)	17 (8.3%)	10 (5.9%)	17 (5.6%)	30 (10.4%)	
Thyroid disorder now	No	45 (24.5%)	5 (35.7%)	3 (33.3%)	7 (43.8%)	12 (42.9%)	0.16
	Yes	139 (75.5%)	9 (64.3%)	6 (66.7%)	9 (56.2%)	16 (57.1%)	
Medication intake	No	1626 (54.9%)	176 (65.4%)	107 (56.3%)	216 (59.8%)	152 (48.9%)	<0.001
	Yes	1338 (45.1%)	93 (34.6%)	83 (43.7%)	145 (40.2%)	159 (51.1%)	

Table 2. Quantitative characteristics of study participants according to work schedule.

	Daytime	**Evening**	**Night**	**Rotating**	**Another**	
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*p-value*
BMI (kg/m^2)	28.53 (6.26)	28.47 (8.29)	28.80 (5.91)	28.28 (6.72)	28.86 (6.88)	0.79
Age (y)	43.19 (14.13)	34.77 (15.89)	38.54 (14.69)	35.73 (15.34)	43.69 (16.54)	<0.001
Iodine (ug/L)	220.88 (622.86)	406.87 (2998.58)	225.05 (2379.97)	2379.97 (40897.23)	223.39 (321.00)	0.04
Hours worked last week	40.58 (13.15)	35.10 (15.22)	42.49 (16.05)	39.43 (18.08)	40.60 (24.38)	<0.001
Poverty ratio	2.27 (1.30)	1.96 (1.29)	1.98 (1.28)	1.96 (1.24)	2.18 (1.38)	<0.001

Note: BMI = Body Mass Index. P-value calculated with ANOVA tests.

Characteristics of the 4,095 participants, who were categorized as daytime workers (2964, 72.38%), evening workers (269, 6.57%), night workers (190, 4.64%), rotating workers (361, 8.82%) and another schedule (311, 7.59%) workers are shown in **Table 1 and Table 2**. The majority of night-shift workers were white, had a College Degree or above and were married. Compared to daytime workers, night shift workers were less likely to be white (33.7% compared to 44.9% white day workers) and were less likely to have a College Degree (36.3% compared to 52.6%). 18% of night-shift workers suffered from sleep problems compared to 17.7% day workers, and 5.8% night shift workers have been diagnosed with sleep disorders compared to 5.7% of day workers. Night shift workers drunk less and had lower physical activity rates than daytime workers (33.8% compared to 38.1%). 31.8% of night-shift workers were current smokers compared to 21.2% of daytime workers. Night shift workers were less likely to have been diagnosed with a thyroid disorder compared to daytime workers (5.9% compared to 6.8%). 43.7% of night workers were on medication compared to 45.1% of the day workers. Except for Body Mass Index (BMI), there was a significant difference across work schedule categories for age, iodine levels, hours worked the previous week and the poverty ratio. The average BMI of night-shift workers was 28.80 kg/m^2 and the average age 38.54 years, compared to 28.53 kg/m^2 and 43.19 years for day workers. Their average iodine level was 225.05 ug/L (compared to 220.88 ug/L for day workers) and they worked 42.49 per week, compared to 40.58 hours for day workers. The average poverty ratio among night shift workers was 1.98, compared to 2.27 for day workers.

Table 3. Average thyroid biomarker levels according to work schedule

	Daytime	**Evening**	**Night**	**Rotating**	**Another**	
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	p-value
TSH (μIU/mL)	1.83 (2.41)	2.04 (2.96)	2.00 (3.48)	1.74 (1.34)	1.90 (1.31)	0.46
ATG(IU/mL)	9.28 (95.27)	17.20 (162.46)	4.67 (45.31)	7.69 (88.51)	6.54 (61.92)	0.63
TPO (IU/mL)	18.51 (82.32)	20.49 (84.78)	20.00 (91.88)	22.51 (97.30)	24.81 (100.57)	0.72
tT3 (ng/dL)	115.96 (28.30)	119.54 (22.91)	120.41 (31.35)	119.53 (22.38)	115.54 (24.04)	0.01
tT4 (ug/dL)	7.84 (1.66)	7.71 (1.53)	7.71 (1.51)	7.87 (1.73)	7.73 (1.47)	0.43
f3F (pg/mL)	3.26 (0.78)	3.34 (0.40)	3.34 (0.52)	3.29 (0.39)	3.26 (0.41)	0.16
f4F (ng/dL)	0.78 (0.19)	0.78 (0.14)	0.76 (0.13)	0.77 (0.16)	0.87 (0.13)	0.48

Note: TSH (Thyroid Stimulating Hormone), ATG (Thyroglobulin Antibodies), TPO (Thyroperoxydase Antibodies), tT3 (Triiodothyronine, total), tT4 (Thyroxine, total), fT3 (Triiodothyronine, free), fT4 (Thyroxine, free).P-values calculated with ANOVA tests.

The distribution of the different thyroid biomarkers across categories for shift work: daytime workers, night workers, rotating workers and another schedule workers are shown in **Table 3.** Night shift workers had significantly higher total Triiodothyronine (tT3) levels than daytime

workers (120 ng/dL compared to 115.96ng/dL). Other thyroid biomarkers did not significantly change across work schedule categories.

Table 4. Average thyroid biomarker levels according to short sleep, regular sleep and long sleep

	Short sleep	**Regular sleep**	**Long sleep**	
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	p-value
TSH (µIU/mL)	1.76 (1.63)	1.89 (2.03)	1.92 (3.38)	0.16
ATG (IU/mL)	9.48 (103.35)	12.16 (105.76)	5.91 (75.73)	0.28
TPO (IU/mL)	18.65 (84.46)	19.97 (84.96)	19.98 (87.05)	0.89
fT3 (ng/dL)	116.41 (26.11)	116.10 (29.93)	117.66 (29.60)	0.33
fT4 (ug/dL)	7.80 (1.65)	7.81 (1.67)	7.85 (1.58)	0.63
t3F (pg/mL)	3.28 (0.85)	3.25 (0.62)	3.26 (0.52)	0.58
t4F (ng/dL)	0.78 (0.18)	0.79 (0.18)	0.79 (0.17)	0.15

Note : short sleep (<6 hours of sleep per night), regular sleep (7 hours sleep per night), long sleep (>8 hours sleep per night). TSH (Thyroid Stimulating Hormone), ATG (Thyroglobulin Antibodies), TPO (Thyroperoxydase Antibodies), tT3 (Triiodothyronine, total), tT4 (Thyroxine, total), fT3 (Triiodothyronine, free), fT4 (Thyroxine, free). P)value calculated with ANOVA tests.

The distribution of thyroid biomarkers across categories of short sleepers (1,665, 40.80%), regular sleepers (1,238, 30.34%) and long sleepers (1,178, 28.87%) are shown in **Table 4**. There was no significant difference between thyroid biomarker levels and sleep duration categories.

8.2. Association of shift work and thyroid biomarkers

Table 5. Linear Regression of thyroid biomarkers and work schedule

Ref = Daytime		**Evening**	**Night**	**Rotating**	**Another**
		β (95%CI)	*β (95%CI)*	*β (95%CI)*	*β (95%CI)*
TSH (µIU/mL)	Model 1	0.30 (0.00, 0.60)	0.22 (-0.13, 0.57)	-0.01 (-0.27, 0.25)	0.07 (-0.21, 0.35)
	Model 2	0.53 (0.11, 0.94)	0.41 (-0.04, 0.85)	0.02 (-0.32, 0.35)	0.05 (-0.29, 0.39)
ATG (IU/mL)	Model 1	0.14 (0.02, 0.27)	0.01 (-0.13, 0.16)	0.03 (-0.08, 0.14)	0.02 (-0.09, 0.14)
	Model 2	0.24 (0.08, 0.39)	0.09(-0.08, 0.27)	-0.01(-0.14, 0.12)	-0.01(-0.15, 0.12)
TPO (IU/mL)	Model 1	0.14 (-0.08, 0.37)	-0.08 (-0.34, 0.18)	-0.01 (-0.21, 0.18)	0.04 (-0.17, 0.24)
	Model 2	0.31 (0.02, 0.60)	0.00 (-0.31, 0.31)	-0.02(-0.26, 0.21)	0.07 (-0.17, 0.31)
tT3 (ng/dL)	Model 1	0.92 (-2.48, 4.32)	2.98 (-0.99, 6.94)	1.20 (-1.77, 4.18)	-0.27 (-3.42, 2.88)
	Model 2	2.18(-2.14, 6.50)	4.36(-0.33, 9.05)	1.43(-2.07, 4.93)	-0.40(-3.95, 3.16)
tT4 (ug/dL)	Model 1	-0.13 (-0.34, 0.07)	-0.13 (-0.37, 0.11)	0.03 (-0.14, 0.21)	-0.11 (-0.30, 0.08)
	Model 2	-0.24(-0.50, 0.01)	0.04(-0.23, 0.32)	0.00(-0.20, 0.21)	0.00(-0.21, 0.21)
fT3 (pg/mL)	Model 1	0.01 (-0.08, 0.09)	0.04 (-0.06, 0.14)	-0.04 (-0.11, 0.04)	-0.03 (-0.11, 0.05)
	Model 2	0.03(-0.09, 0.14)	0.07 (-0.05, 0.20)	-0.02(-0.12, 0.07)	-0.01(-0.10, 0.08)

fT4 (ng/dL)	Model 1	-0.01 (-0.03, 0.82)	-0.02 (-0.05, 0.00)	-0.01 (-0.03, 0.01)	-0.00 (-0.02, 0.02)
	Model 2	-0.03(-0.06, 0.00)	-0.02(-0.05, 0.01)	-0.02(-0.04, 0.00)	0.00(-0.02, 0.03)

Note: Model 1 (ag- adjusted), Model 2 (adjusted for age, gender, ethnicity and alcohol consumption)

The results from the linear regression are shown in **Table 5**. Transformation of beta coefficient of ATG and TPO are seen in Appendix 12.7. Evening workers had an increase of 0.53 µIU/mL (IC: 0.11,0.94) of their TSH levels compared to daytime workers, in the multi-variable adjusted model. There was also an increase of TSH levels found in the age-adjusted model (0.30 µIU/mL for evening workers), however, these results were not significant. No significant difference was found between night workers and day workers. People working evening shifts had 15.02% higher ATG levels compared to daytime workers in the age-adjusted model (95%CI: 2.02,31.00) and 27.12% higher ATG levels in the multi-variable adjusted model (95%CI: 8.33,46.23). However, no significant difference was found between night workers and day workers. TPO, tT3, tT4, fT3 and fT4 levels were not significantly different across the shift work schedule categories compared to daytime workers.

8.3. Association of sleep duration with thyroid biomarkers

Table 6. Linear Regression of thyroid biomarker levels and sleep duration

Ref = regular sleep		**Short sleep**	**Long sleep**
		β (95%CI)	*β (95%CI)*
TSH (µIU/mL)	Model 1	-0.13 (-0.31, 0.04)	0.06 (-0.13, 0.25)
	Model 2	-0.06 (-0.27, 0.16)	0.06 (-0.18, 0.29)
ATG (IU/mL)	Model 1	-0.06 (-0.13, 0.01)	-0.06 (-0.14, 0.02)
	Model 2	0.02 (-0.06, 0.11)	-0.04 (-0.13, 0.05)
TPO (IU/mL)	Model 1	-0.08 (-0.21, 0.05)	-0.06 (-0.20, 0.08)
	Model 2	-0.06 (-0.21, 0.09)	-0.12 (-0.28, 0.04)
TT3 (ng/dL)	Model 1	0.50 (-1.49, 2.48)	0.94 (-1.22, 3.09)
	Model 2	-0.20 (-2.46, 2.05)	0.46 (-1.98, 2.89)
TT4 (ug/dL)	Model 1	-0.02 (-0.14, 0.10)	0.04 (-0.09, 0.17)
	Model 2	-0.23 (-0.16, 0.11)	0.03 (-0.12, 0.17)
T3F (pg/mL)	Model 1	0.03 (-0.02, 0.08)	-0.01 (-0.06, 0.05)
	Model 2	0.02 (-0.04, 0.08)	-0.02 (-0.08, 0.05)
T4F (ng/dL)	Model 1	-0.01 (-0.02, 0.00)	0.00 (-0.01, 0.02)
	Model 2	-0.01 (-0.03, 0.00)	-0.00 (-0.02, 0.01)

Note: Model 1 (age-adjusted), Model 2 (adjusted for age, gender, ethnicity and alcohol consumption). Short sleep <6 hours, long sleep >8 hours.

The result of the association between thyroid biomarkers and sleep duration are shown in **Table 6**. There was no significant biomarker level difference between night shift workers and daytime workers.

8.4. Biomarkers, self-reported sleep problems and diagnosed sleep disorders

Table 7. Linear Regression of thyroid biomarker levels, self-reported sleep problems and diagnosed sleep problems.

Ref = No		**Self-reported sleep problems**	**Diagnosed sleep disorder**
		β (95%CI)	*β (95%CI)*
TSH (µIU/mL)	Model 1	0.08 (-0.11, 0.27)	0.02 (-0.29, 0.34)
	Model 2	-0.01 (-0.24, 0.22)	-0.11 (-0.49, 0.27)
ATG (IU/mL)	Model 1	-0.05 (-0.13, 0.03)	-0.06 (-0.19, 0.07)
	Model 2	-0.07 (-0.16, 0.02)	-0.05 (-0.19, 0.10)
TPO (IU/mL)	Model 1	0.05 (-0.09, 0.19)	-0.08 (-0.31, 0.16)
	Model 2	0.00 (-0.15, 0.17)	-0.09 (-0.35, 0.18)
tT3 (ng/dL)	Model 1	-2.26 (-4.42, -0.09)	-3.48 (-7.07, 0.10)
	Model 2	-1.62 (-4.03, 0.79)	-3.00 (-6.95, 0.94)
tT4 (ug/dL)	Model 1	-0.11 (-0.23, 0.03)	0.00 (-0.30, 0.14)
	Model 2	-0.11 (-0.25, 0.03)	0.12 (-0.18, 0.35)
fT3 (pg/mL)	Model 1	-0.09 (-0.14, -0.03)	-0.07 (-0.16, 0.02)
	Model 2	-0.04 (-0.11, 0.02)	-0.05 (-0.15, 0.06)
fT4 (ng/dL)	Model 1	-0.01 (-0.02, 0.00)	0.00 (-0.02, 0.00)
	Model 2	-0.01 (-0.03, 0.01)	0.01 (-0.01, 0.04)

Note: Model 1 (age-adjusted), Model 2 (adjusted for age, gender, ethnicity and alcohol consumption)

Results of the general linear models are shown in **Table 7**. People reporting sleep problems presented a decrease of 2.26 ng/mL (95%CI: -4.42, -0.09) in their tT3 levels and a decrease of 0.09 pg/mL (95%CI : -0.14, -0.03) in their fT3 levels compared to people without self-reported sleep problems, in the age-adjusted model. The multi-variable model also showed a decrease in tT3 and fT3 levels as well for people reporting sleep problems (-1.62 ng/mL and -0.04 pg/mL), yet results were not significant. People diagnosed with sleep disorder did not experience any significant thyroid biomarker variation. The three models for TSH, TPO, ATG, tT4 and fT4 did not show any significant difference.

8.5. Effect Modification of the association of work schedule with thyroid biomarkers

The effect modification was assessed with the multi-variable adjusted model (Model 2).

8.5.1. Effect Modification by gender

Table 8. Examination of the Effect Modification by gender according to work schedule.

Ref = Daytime		**Evening**	**Night**	**Rotating**	**Another**
		β (95%CI)	*β (95%CI)*	*β (95%CI)*	*β (95%CI)*
TSH (μIU/mL)	Male	0.10 (-0.13, 0.32)	-0.07 (-0.32, 0.18)	-0.09 (-0.30, 0.11)	0.11 (-0.09, 0.32)
	Female	0.34 (-0.24, 0.92)	0.52 (-0.21, 1.24)	-0.10 (-0.58, 0.39)	0.03 (-0.53, 0.59)
ATG (IU/mL)	Male	-0.05 (-0.20, 0.10)	-0.06 (-0.22, 0.11)	-0.05 (-0.18, 0.09)	0.00 (-0.13, 0.14)
	Female	0.27 (0.06, 0.47)	0.07 (-0.18, 0.33)	0.01 (-0.16, 0.18)	0.05 (-0.14, 0.25)
TPO (IU/mL)	Male	-0.20 (-0.46, 0.06)	-0.36 (-0.65, -0.06)	-0.10 (-0.34, 0.14)	0.05 (-0.19, 0.29)
	Female	0.41 (0.04, 0.78)	0.26 (-0.19, 0.72)	-0.07 (-0.37, 0.24)	0.03 (-0.32, 0.38)
tT3 (ng/dL)	Male	4.36 (0.81, 7.90)	4.44 (0.46, 8.43)	4.33 (1.07, 7.58)	0.37 (-2.88, 3.63)
	Female	2.73 (-3.37, 8.83)	4.27 (-3.31, 11.85)	3.08 (-2.00, 8.16)	-1.46 (-7.30, 5.37)
tT4 (ug/dL)	Male	-0.06 (-0.31, 0.19)	0.00 (-0.28, 0.28)	-0.03 (-0.26, 0.20)	0.09 (-0.14, 0.32)
	Female	-0.22 (-0.54, 0.10)	-0.24 (-0.64, 0.16)	0.02 (-0.25, 0.28)	-0.35 (-0.65, -0.04)
fT3 (pg/mL)	Male	0.10 (0.04, 0.17)	0.07 (0.01, 0.14)	0.06 (0.01, 0.12)	0.00 (-0.06, 0.06)
	Female	0.06 (-0.11, 0.23)	0.07 (-0.14, 0.28)	0.02 (-0.12, 0.17)	-0.08 (-0.24, 0.09)
fT4 (ng/dL)	Male	-0.00 (-0.02, 0.02)	-0.12 (-0.04, 0.01)	0.01 (-0.01, 0.03)	0.02 (-0.00, 0.04)
	Female	-0.01 (-0.05, 0.03)	-0.02 (-0.08, 0.02)	-0.03 (-0.06, 0.00)	-0.03 (-0.06, 0.01)

Table 8 shows the stratified analysis results by gender. ATG and TPO transformations are seen in Appendix 12.7. Female evening workers, compared with female day-time workers, had an increase of 31% (95%CI: 6.18, 60.00) of ATG levels, and an increase of 50.68% (95%CI: 4.08,118.15) of TPO levels. However, no significant difference in these biomarkers was observed between night and day workers, consistently across male and female workers. Male night shift workers had 30% (95%CI: -47.80, -5.82) lower TPO levels compared to male day shift workers. Male night shift workers had an increase of 4.44 ng/dL (95%CI: 0.46,8.43) of their tT3 levels and an increase of 0.07 pg/dL (95%CI: 0.01,0.14) of their fT3 levels compared with male daytime workers. Male evening workers had an increase of 4.36 ng/dL (95%CI: 0.81,7.90) of their tT3 levels and an increase of 0.10 pg/dL (95%CI: 0.04,0.17) of their fT3 levels

compared with males working daytime. Male rotating shift workers had an increase of 4.33 ng/dL (95%CI: 1.07,7.58) of their tT3 levels and an increase of 0.06 pg/dL (95%CI: 0.01,0.14) of their fT3 levels compared with male day workers. Neither males nor females working on "another schedule" had significantly tT3 and fT3 different levels.

8.5.2. Effect Modification by ethnicity

Table 9. Linear Regression of thyroid biomarkers and work schedule by ethnicity

Ref = Daytime		**Evening**	**Night**	**Rotating**	**Another**
		β (95%CI)	*β (95%CI)*	*β (95%CI)*	*β (95%CI)*
TSH (µIU/mL)	White	0.09 (-0.48, 0.66)	0.79 (0.06, 1.53)	-0.19 (-0.71, 0.32)	0.10 (-0.37, 0.56)
	Black	0.26 (-0.01, 0.53)	-0.00 (-0.29, 0.28)	0.05 (-0.19, 0.29)	-0.17 (-0.45, 0.10)
	Mexican American	0.87 (0.12, 1.62)	-0.08 (-0.87, 0.70)	-0.01 (-0.56, 0.55)	0.10 (-0.70, 0.90)
ATG (IU/mL)	White	0.01 (-0.20, 0.23)	-0.21 (-0.49, 0.08)	0.08 (-0.12, 0.27)	-0.00 (-0.18, 0.18)
	Black	0.07 (-0.11, 0.25)	0.10 (-0.09, 0.29)	0.09 (-0.06, 0.25)	-0.01 (-0.19, 0.17)
	Mexican American	0.32 (0.02, 0.62)	0.13 (-0.19, 0.45)	-0.20 (-0.43, 0.02)	0.05 (-0.27, 0.38)
TPO (IU/mL)	White	-0.03 (-0.39, 0.32)	-0.30 (-0.77, 0.16)	0.08 (-0.25, 0.40)	0.13 (-0.16, 0.43)
	Black	0.18 (-0.19, 0.55)	0.06 (-0.33, 0.45)	-0.00 (-0.33, 0.32)	-0.10 (-0.47, 0.27)
	Mexican American	0.38 (-0.20, 0.96)	-0.06 (-0.67, 0.54)	-0.10 (-0.53, 0.33)	0.30 (-0.32, 0.91)
tT3 (ng/dL)	White	5.58 (1.27, 9.89)	6.92 (1.27, 12.57)	4.02 (0.07, 7.97)	0.92 (-2.66, 4.50)
	Black	1.13 (-6.51, 9.11)	-1.18 (-9.53, 7.18)	1.34 (-5.57, 8.24)	-5.26 (-13.18, 2.66)
	Mexican American	2.37 (-4.38, 9.11)	7.49 (0.04, 14.57)	6.80 (1.80, 11.79)	-1.59 (-8.75, 5.58)
tT4 (ug/dL)	White	-0.11 (-0.39, 0.18)	0.18 (-0.20, 0.55)	0.08 (-0.19, 0.34)	-0.02 (-0.26, 0.22)
	Black	0.13 (-0.36, 0.63)	-0.72 (-1.25, -0.19)	-0.06 (-0.50, 0.37)	-0.25 (-0.75, 0.24)
	Mexican American	-0.23 (-0.70, 0.25)	-0.02 (-0.52, 0.48)	0.16 (-0.20, 0.51)	-0.06 (-0.56, 0.45)
fT3 (pg/mL)	White	0.15 (0.08, 0.23)	0.17 (0.07, 0.26)	0.05 (-0.02, 0.12)	0.02 (-0.04, 0.09)
	Black	0.02 (-0.17, 0.21)	0.01 (-0.19, 0.21)	0.03 (-0.13, 0.20)	-0.08 (-0.27, 0.11)
	Mexican American	0.05 (-0.26, 0.35)	0.01 (-0.31, 0.33)	-0.01 (-0.24, 0.21)	-0.09 (-0.42, 0.23)
fT4 (ng/dL)	White	-0.01 (-0.03, 0.02)	0.02 (-0.02, 0.55)	-0.01 (-0.04, 0.01)	0.01 (-0.01, 0.03)
	Black	-0.01 (-0.08, 0.05)	-0.05 (-0.12, 0.02)	-0.03 (-0.09, 0.03)	-0.03 (-0.10, 0.03)
	Mexican American	0.00 (-0.04, 0.05)	-0.03 (-0.08, 0.02)	0.04 (-0.00, 0.07)	0.00 (-0.05, 0.05)

As is the case for gender, stratification was performed to examine effect modification by ethnicity. Due to the low rate of participants in the "Other Hispanic" and "Other Ethnicity" categories, stratification was only performed for "white", "black" and "Mexican-American". Results are shown in **Table 9**. ATG and TPO transformations are seen in Appendix 12.7.

White people working night shifts had an increase of 0.79 µIU/mL (95%CI: 0.06, 1.53) of their TSH levels compared with daytime workers. Mexican-American people working on evening shifts had an increase of 0.87 µIU/mL (95%CI: 0.12, 1.62) of TSH levels compared with daytime workers. Black people working any shift did not show any significant TSH difference compared to daytime work. Mexican American people working evening shifts had an increase of 37.71 % (95%CI: 2.02, 85.89) of ATG levels when compared with Mexican-American day workers. White and black people working any schedule showed no significant ATG level difference. White people working evening, night and rotating shifts had an increased level of tT3 compared with daytime workers. For the evening shift, an increase of 5.58 ng/dL (95%CI: 1.27, 9.89), for night shift workers an increase of 6.92 ng/dL (95%CI: 1.27, 12.57) and for rotating shift workers an increase of 4.02 ng/dL (95%CI: 0.07, 7.97). Mexican American people working night shifts and rotating shifts also had increased fT3 levels compared with Mexican-American daytime workers. Night shift workers had an increase of 7.49 ng/dL (95%CI: 0.04, 14.57) and rotating shift workers had an increase of 6.80 ng/dL (95%CI: 1.80, 11.79). Black people working any work schedule showed no significant fT3 level difference. Black people working night shifts had a decrease of 0.72 ug/dL (95%CI: -1.25,-0.19) of their tT4 levels compared with black daytime workers. White and Mexican-American people working any shift showed no significant difference in tT4 levels. White people working evening and night shifts presented a significant difference in their fT3 levels compared with white daytime workers. Evening workers had an increase of 0.13 pg/mL (95%CI: 0.08, 0.23) and night workers had an increase of 0.17 pg/mL (95%CI: 0.07, 0.26). Black and Mexican-American people working any shift exhibited no significant fT3 level difference. Ethnicity had no significant impact on fT4 levels or on TPO levels.

8.5.3. Effect Modification by sleep duration

Table 10. Linear Regression of thyroid biomarkers and work schedule by sleep duration

Ref = Daytime		**Evening**	**Night**	**Rotating**	**Another**
		β (95%CI)	*β (95%CI)*	*β (95%CI)*	*β (95%CI)*
TSH (µIU/mL)	Short sleep	-0.13 (-0.04, 0.19)	-0.08 (-0.38, 0.23)	0.04 (-0.24, 0.31)	0.05 (-0.24, 0.34)
	Regular sleep	0.07 (-0.40, 0.54)	0.29 (-0.38, 0.97)	-0.22 (-0.66, 0.22)	0.11 (-0.21, 0.44)
	Long sleep	0.39 (-0.36, 1.14)	2.45 (0.58, 4.32)	-0.19 (-0.84, 0.47)	0.01 (-0.78, 0.81)
	Short sleep	-0.08 (-0.27, 0.11)	0.03 (-0.16, 0.21)	0.03 (-0.13, 0.20)	0.04 (-0.13, 0.22)

ATG	Regular sleep	0.37 (-0.00, 0.65)	-0.09 (-0.51, 0.33)	-0.12 (-0.36, 0.11)	0.05 -0.18, 0.27)
(IU/mL)	Long sleep	0.10 (-0.10, 0.31)	-0.02 (-0.31, 0.27)	0.04 (-0.31, 0.27)	-0.04 (-0.25, 0.18)
TPO	Short sleep	-0.11 (-0.45, 0.24)	-0.17 ()0.50, 0.16)	-0.16 (-0.46, 0.14)	-0.00 '-0.32, 0.32)
(IU/mL)	Regular sleep	0.46 (0.02, 0.90)	0.30 (-0.38, 0.98)	-0.08 (-0.47, 0.31)	0.26 (-0.11, 0.63)
	Long sleep	0.16 (-0.40, 0.71)	-0.20 (-0.77, 0.37)	0.09 (-0.25, 0.44)	-0.17 (-0.59, 0.25)
tT3	Short sleep	7.14 (0.79, 13.51)	3.76 (-1.11, 8.63)	1.52 (-2.84, 5.89)	-0.64 (-5.28, 4.00)
(ng/dL)	Regular sleep	2.28 (-4.35, 8.90)	7.53 (-2.77, 17.83)	2.87 (-3.01, 8.75)	-2.05 (-7.65, 3.54)
	Long sleep	1.91 (-4.68, 8.49)	5.01 (-4.47, 14.49)	7.43 (1.68, 13.18)	2.01 (-4.96, 8.99)
tT4	Short sleep	-0.24 (-0.56, 0.08)	0.17 (-0.48, 0.13)	-0.04 (-0.32, 0.23)	0.01 (-0.29, 0.29)
(ug/dL)	Regular sleep	0.21 (-0.20, 0.62)	0.12 (-0.52, 0.76)	-0.13 (-0.50, 0.23)	-0.32 (-0.67, 0.03)
	Long sleep	-0.26 (-0.61, 0.09)	-0.11 (-0.62, 0.40)	0.28 (-0.03, 0.58)	-0.10 (-0.47, 0.27)
fT3	Short sleep	0.04 (-0.13, 0.20)	0.06 (-0.10, 0.22)	0.01 (-0.13, 0.15)	-0.03 (-0.19, 0.11)
(pg/mL)	Regular sleep	0.07 (-0.08, 0.22)	0.11 (-0.13, 0.35)	0.03 (-0.10, 0.17)	-0.06 (-0.19, 0.07)
	Long sleep	0.03 (-0.12, 0.19)	0.08 (-0.09, 0.24)	0.07 (-0.04, 0.17)	0.01 (-0.12, 0.13)
fT4	Short sleep	-0.03 (-0.07, 0.00)	-0.01 (-0.05, 0.02)	-0.02 (-0.05, 0.01)	0.01 (-0.03, 0.04)
(ng/dL)	Regular sleep	-0.00 (-0.04, 0.04)	-0.03 (-0.10, 0.02)	-0.02 (-0.05, 0.02)	-0.02 (-0.06, 0.02)
	Long sleep	0.02 (-0.01, 0.06)	-0.01 (-0.07, 0.04)	0.01 (-0.03, 0.39)	0.01 (-0.03, 0.05)

Note : Short sleep <6hours, Regular seep : 7hours, Long sleep >8 hours.

Results of the stratification to examine effect modification by sleep duration are shown in **Table 10**. Transformation of ATG and TPO are seen in Appendix 12.7. Night shift workers who had more than 8 hours sleep per night had an increase of 2.45 µIU/mL (95%CI: 0.58,4.32) of their TSH levels compared to day workers with more than 8 hours sleep per night. Evening workers with 7 hours sleep at night had 58.41% (95%CI: 2.02, 145,96) higher TPO levels than daytime workers with the same amount of sleep at night. Night shift work was not associated with TPO levels. Evening workers with less than 6 hours sleep at night had an increase of 7.14 ng/dL (95%CI: 0.79, 13.51) of their tT3 levels compared to day workers with the same amount of sleep. Sleep duration did not significantly modify the association between shift work and tT4, fT3 or ATG levels.

8.5.4. Effect Modification by self-reported sleep problems

Table 11. Linear Regression of thyroid biomarkers and work schedule by sleep problems

Ref = Daytime		**Evening**	**Night**	**Rotating**	**Another**
		β (95%CI)	*β (95%CI)*	*β (95%CI)*	*β (95%CI)*
TSH	Yes	0.13 (-0.47, 0.73)	0.42 (-0.21, 1.05)	-0.45 (-0.92, 0.01)	-0.03 (-0.46, 0.39)
(µIU/mL)	No	0.23 (-0.10, 0.56)	0.12 (-0.28, 0.52)	0.01 (-0.31, 0.29)	0.09 (-0.24, 0.43)
ATG	Yes	0.24 (-0.06, 0.54)	0.07 (-0.24, 0.39)	0.06 (-0.17, 0.30)	0.15 (-0.07, 0.36)
(IU/mL)	No	0.07 (-0.06, 0.21)	-0.02 (-0.19, 0.14)	-0.03 (-0.15, 0.09)	-0.01 (-0.15, 0.12)
	Yes	0.09 (-0.53, 0.72)	0.19 (-0.47, 0.85)	0.11 (-0.37, 0.59)	-0.01 (-0.45, 0.43)

TPO (IU/mL)	No	0.09 (-0.15, 0.33)	-0.17 (-0.46, 0.11)	-0.10 (-0.31, 0.11)	0.05 (-0.19, 0.29)
tT3 (ng/dL)	Yes	6.26(-2.48, 15.00)	7.82 (-1.84, 17.50)	-0.35 (-7.40, 6.63)	3.09 (-3.03, 9.21)
	No	3.30 (-0.51, 7.11)	3.65 (-0.93, 8.23)	3.92 (0.50, 7.33)	-2.31 (-6.13, 1.51)
tT4 (ug/dL)	Yes	-0.26 (-0.59, 0.44)	-0.14 (-0.77, 0.33)	-0.23 (-0.62, 0.19)	-0.64 (-1.05, -0.23)
	No	-0.14 (-0.36, 0.08)	-0.10 (-0.37, 0.17)	0.09 (-0.11, 0.29)	-0.01 (-0.24, 0.21)
fT3 (pg/mL)	Yes	0.15 (-0.45, 0.75)	0.17 (0.05, 0.30)	0.06 (-0.03, 0.16)	0.09 (-0.00, 0.17)
	No	-0.01 (-0.12, 0.11)	0.05 (-0.08, 0.19)	-0.01 (-0.11, 0.09)	-0.01 (-0.12, 0.09)
fT4 (ng/dL)	Yes	0.02 (-0.03, 0.07)	-0.03 (-0.08, 0.02)	-0.02 (-0.05, 0.02)	-0.03 (-0.06, 0.01)
	No	-0.01 (-0.04, 0.01)	-0.02 (-0.05, 0.01)	-0.01 (-0.03, 0.01)	0.01 (-0.02, 0.03)

Results of the stratification to examine effect modification by self-reported sleep problems are shown in **Table 11.** No transformation of ATG and TPO was needed as they do not present any significant results with sleep problems. People working another schedule with sleep problems presented a decrease of 0.64 ug/dL (95%: -1.05,-0.23 of their tT4 levels compared to day workers with sleep problems. No effect modification was found by sleep problems for TSH, fT3, tT3, tT4 or fT4.

8.6. Logistic Regression on clinically significant thyroid biomarker levels and work schedule

Table 12. Logistic Regression of clinically significant thyroid biomarker levels and work schedule

Ref = Daytime		**Evening**	**Night**	**Rotating**	**Another**
		OR (95%CI)	*OR (95%CI)*	*OR (95%CI)*	*OR (95%CI)*
Low vs. normal TSH (µIU/mL)	Model 1	0.46 (0.15, 1.53)	0.86 (0.31, 2.38)	0.69 (0.30, 1.61)	0.25 (0.06, 1.03)
	Model 2	0.53 (0.13, 2.19)	0.91 (0.28, 2.98)	0.31 (0.07, 1.28)	0.32 (0.08, 1.33)
High vs. normal TSH (µIU/mL)	Model 1	1.77 (0.83, 3.80)	0.89 (0.28, 2.89)	0.97 (0.41, 2.29)	1.67 (0.84, 3.31)
	Model 2	2.25 (0.94, 5.40)	0.92 (0.22, 3.85)	0.90 (0.32, 2.54)	1.62 (0.75, 3.51)
ATG positivity vs. non (IU/mL)	Model 1	1.91 (1.17, 2.97)	1.30 (0.67, 2.29)	1.31 (0.80, 2.04)	1.47 (0.91, 2.26)
	Model 2	2.45 (1.35, 5.16)	1.77 (0.84, 3.22)	1.29 (0.71, 2.19)	1.23 (0.68, 2.09)
TPO positivity vs. non (IU/mL)	Model 1	1.61 (1.09, 2.13)	0.93 (0.54, 1.51)	1.17 (0.80, 1.65)	1.05 (0.70, 1.51)
	Model 2	2.06 (1.29, 3.19)	1.03 (0.53, 1.83)	1.13 (0.72, 1.72)	1.16 (0.75, 1.73)
Low fT3 vs. normal (pg/mL)	Model 1	1.19 (0.19, 4.04)	2.24 (0.53, 6.50)	1.29 (0.31, 3.73)	1.65 (0.55, 4.03)
	Model 2	1.90 (0.29, 6.81)	1.23 (0.07, 6.19)	1.04 (0.16, 3.65)	1.53 (0.43, 4.18)

Low fT4 vs. normal (ng/dL)	Model 1	0.95 (0.33, 2.17)	1.27 (0.44, 2.91)	1.41 (0.67, 2.66)	1.12 (0.49, 1.03)
	Model 2	1.19 (0.35, 2.99)	1.09 (0.26, 3.03)	1.50 (0.65, 3.06)	1.30 (0.53, 3.74)

Note : Note: Model 1 (age-adjusted), Model 2 (adjusted for age, gender, ethnicity and alcohol consumption) Low TSH <0.34, high TSH >5.6, low fT3 as <2.5 pg/mL, low fT4 as < 0.6 ng/dL, Antibody positivity as TPO>9.0 IU/mL and ATG>4.0 IU/mL.

Continuous biomarker variables were transformed into binary outcomes according to clinical cut-offs. A Logistic Regression was constructed to assess any association between clinically relevant biomarker levels and night-shift workers. Odds ratio and 95%CI have been estimated, which can reveal the odds that an outcome will occur in the presence of an exposure compared to the odds of the outcome occurring in the absence of the exposure. Results are shown in **Table 12**. In the age-adjusted model, there was a 91% (95%CI: 1.17,2.97) chance of people working in the evening having ATG positivity when compared with daytime workers. In the multi-variable adjusted model, people working in the evening had a 2.5-fold higher chance (95%CI: 1.35,5.16) of having ATG positivity than daytime workers. No other work schedules resulted in higher odds of having ATG positivity.

In the age-adjusted model, people working in the evening had a 61% higher chance of having TPO positivity compared with daytime workers. In the multi-variable adjusted model, people working in the evening had a 2-fold higher chance (95%CI: 1.29,3.19) of TPO positivity than people working during the day. The other biomarkers did not vary significantly across work schedule categories.

8.7. Sensitivity Analysis

Table 13. Linear Regression of thyroid biomarkers and work schedule after exclusion of people with thyroid disease and people on medication (sensitivity analysis)

Ref = Daytime		**Evening**	**Night**	**Rotating**	**Another**
		β (95%CI)	*β (95%CI)*	*β (95%CI)*	*β (95%CI)*
TSH (µIU/mL)	Model 1	0.54 (0.28, 0.81)	0.03 (-0.30, 0.36)	-0.01 (-0.25, 0.24)	-0.05 (-0.33, 0.02)
	Model 2	0.88 (0.49, 1.26)	0.12 (-0.34, 0.58)	-0.05 (-0.38, 0.27)	-0.05 (-0.42, 0.32)
ATG (IU/mL)	Model 1	0.11 (-0.03, 0.25)	0.02 (-0.15, 0.20)	0.01 (-0.12, 0.13)	-0.04 (-0.189, 0.11)
	Model 2	0.12 (-0.05, 0.30)	0.14 (-0.07, 0.35)	-0.07 (-0.23, 0.08)	-0.02 (-0.19, 0.15)
TPO (IU/mL)	Model 1	0.12 (-0.14, 0.38)	0.05 (-0.28, 0.37)	0.10 (-0.14, 0.43)	-0.10 (-0.38, 0.18)

	Model 2	0.35 (0.01, 0.69)	0.03 (-0.38, 0.44)	0.07 (-0.22, 0.36)	0.05 (-0.28, 0.38)
tT3 (ng/dL)	Model 1	0.65 (-3.56, 4.87)	3.22 (-2.02, 8.46)	1.23 (-2.62, 5.08)	-1.44 (-5.92, 3.04)
	Model 2	3.34 (-1.92, 8.59)	4.74 (-1.59, 11.08)	2.40 (-2.10, 6.91)	-0.13 (-5.24, 4.97)
tT4 (ug/dL)	Model 1	-0.17 (-0.43, 0.08)	-0.25 (-0.56, 0.07)	0.16 (-0.08, 0.39)	-0.32 (-0.30, 0.24)
	Model 2	-0.22 (-0.54, 0.10)	0.02 (-0.36, 0.41)	0.20 (-0.08, 0.47)	0.16 (-0.15, 0.47)
fT3 (pg/mL)	Model 1	-0.02 (-0.15, 0.11)	0.04 (-0.12, 0.20)	-0.04 (-0.15, 0.08)	-0.04 (-0.18, 0.09)
	Model 2	0.02 (-0.15, 0.20)	0.11 (-0.10, 0.32)	-0.00 (-0.18, 0.16)	-0.01 (-0.35, 0.09)
fT (ng/dL)	Model 1	-0.01 (-0.03, 0.02)	-0.02 (-0.06, 0.01)	-0.00 (-0.03, 0.02)	-0.01 (-0.02, 0.04)
	Model 2	-0.02 (-0.05, 0.02)	-0.01 (-0.05, 0.03)	0.00 (-0.03, 0.03)	0.02 (-0.02, 0.05)

Note : Model 1 (age- adjusted), Model 2 (adjusted for age, gender, ethnicity and alcohol consumption)

A sensitivity analysis was carried out on the database by excluding people with thyroid diseases and people on medication. GLMs were performed with three different regression models after exclusion. Results are shown in **Table 13**. Evening workers had 0.54 µIU/mL, (95%CI: 0.28,0.81) higher TSH levels than daytime workers in the age-adjusted model. In the multi-variable adjusted model, evening workers had 0.88 µIU/mL (95%CI: 0.49,1.26) higher TSH levels compared to daytime workers. There was no significant variation in TSH levels among other work schedules. TPO levels were 41.91% (95%CI: 1.01,99.37) higher among evening shift workers compared with daytime workers in the multi-variable adjusted model. However, there was no variation among other work schedules. ATG, tT4, tT3, ft4 and fT3 levels were not associated with night shift work status.

IX. Discussion

Night shift work has been associated with higher risk for thyroid disease and altered thyroid hormone levels [23]. Poor sleep quality has been associated with higher risk for thyroid cancer [23]. This exploratory study provides evidence of the possible alterations of five thyroid biomarkers (ATG, TPO, TSH, fT3, fT4, tT3 and tT4) in relation to circadian and sleep disruption. Previous studies examined night shift work and TSH levels, but rarely studies have evaluated the impact of night shift work and sleep on five thyroid biomarkers. This cross-sectional study

evaluated the association between night shift work and sleep on five thyroid biomarkers as well as joint effects of shift work and sleep in a large US population-based study.

9.1. Work schedule and thyroid biomarkers

Past studies have demonstrated increased TSH levels in people working at night [23]. A study from South Korea showed that people working shifts have higher risk of suffering from subclinical hypothyroidism, with higher TSH levels [50]. Another study, a systematic review, found that "thyroid diseases are more prevalent among night shift workers", as they experience higher TSH levels [51]. A study conducted on nurses and evaluating thyroid hormones showed no difference in T3 and TSH levels in rotating shifts compared to morning shifts, but a significant increase of T4 levels in rotating shifts [52]. A study evaluating shift work and thyroid antibodies showed that there is a higher prevalence of ATG and TPO in shift workers compared to day workers [53]. Another study evaluating female stewardesses and thyroid biomarkers found that, compared to a control group, their thyroid antibody levels (ATG and TPO) and their TSH levels were significantly increased [54].

Our results showed that people working in evening shifts were more likely to develop hypothyroidism, as indicated by increased TSH levels. These results persisted after adjusting for multiple confounders. This was not confirmed by the clinical cut-off analysis, where evening workers had no significantly higher odds of high or low TSH levels (Low TSH <0.34 µIU/mL, high TSH >5.6 µIU/mL). In addition to TSH, evening workers experienced higher ATG levels, in the age and multi-variable adjusted model. This was confirmed by the cut-off analysis, where evening workers had increased risk of ATG and TPO positivity (antibody positivity: TPO>9.0 IU/mL and ATG>4.0 IU/mL) compared to daytime workers. However, no altered thyroid biomarker levels were found in relation to night shift work, neither in the work schedule and biomarker regression, nor in the cut-off analysis.

Our results are consistent with what is found on thyroid antibodies, but not the other biomarkers. The reason could be the fact that other studies have only evaluated female workers, whereas our analysis comprised of males and females. It could also reside in the fact that studies have only evaluated rotating/night shifts compared to day shift, but we

categorized shift work as day shift, night shifts, evening shift, rotating shifts, and another shift schedule.

9.2. Sleep and thyroid biomarkers

Several studies have evaluated the association between sleep and thyroid function and found an effect of sleep on TSH secretion. Sleep deprivation leads to increased TSH, T3 and T4 levels, with TSH levels remaining high throughout the following day [55]. Some studies have evaluated the effect of sleep deprivation as extreme, short-term sleep deprivation, on the TSH circadian rhythm and found increased TSH secretion after short sleep or sleep deprivation. On the other hand, other studies, like a randomized study conducted by Kessler et al. [56] examined whether short sleep (defined as 5 to 6 hours sleep per night) has an impact on the thyroid axis and their results showed a slightly reduced TSH and T4 level in short sleepers. These studies have been conducted on a small number of participants, therefore a larger population would be interesting, like a nationally representative study. Such a study was conducted in China and found that sleep duration is associated with thyroid dysfunction, like subclinical hyperthyroidism or hypothyroidism [57]. In fact, sleeping too long or sleeping too short can both increase the risk of thyroid problems [57].

In the present study no significant association was found between thyroid biomarker levels and sleep duration. The difference with our study might result from the fact that sleep duration is self-reported and not objectively measured as in a randomized study. Because our methodology was quite the same as the nationally representative study, the different results might be explained by differences in the characteristics (e.g. sociodemographic, lifestyle, etc.) of the study population.

Sleep disorders such as insomnia, sleep apnea or even restless leg syndrome can often co-occur with thyroid dysfunctions [31]. A study conducted by Lou et al. showed that elderly people with poor sleep quality had higher risk of suffering from thyroid nodules [32]. Another study on postmenopausal women showed that those with insomnia had higher risk of thyroid cancer compared to other women. However, this study did not find any significant association between sleep duration and thyroid cancer [58].

Our results showed that in the age-adjusted model, having sleep problems was associated with decreased tT3 levels and fT3 levels and thus an increased risk of hypothyroidism. The multi-variable adjusted model did not show any difference, which shows that confounders might have played a role in the significant association found in the age-adjusted model. We might not have found similar results as in the previous two studies because we analyzed a different study population (males and females).

9.3. Secondary analyses: effect modification by gender and ethnicity

A stratification by gender was performed to analyze whether or not gender plays a role in differences of thyroid biomarker levels between day and night workers. Our results of higher TSH levels after evening and night work were stronger among women. Several previous studies conducted among women showed that those who work night shift or rotating shifts have higher risk of suffering from thyroid problems than women working regular day shifts [52,54]. Another study only among women showed that night shift work can disturb women's hormones in addition to alter their circadian rhythm, and thus be more vulnerable to changes in TSH levels [59]. To some extent our study extends these findings to men. Our study showed that males working evening, nights and rotating shift are more at risk of suffering from hyperthyroidism than male day workers as indicated by increased fT3 and tT3 level. Males working evenings were also more likely to suffer from autoimmune thyroiditis, given significantly higher TPO levels. Similarly, females working evening shifts were also more likely to suffer from autoimmune thyroiditis, with higher ATG or TPO levels compared to female day shift workers.

We also evaluated effect modification by ethnicity and found consistent findings across ethnicity and slightly stronger effects among White and Mexican American study participants. A study conducted among US military personnel found that African Americans were more at risk to develop hyperthyroidism (Graves's disease) and white people were more likely to suffer from hypothyroidism (Hashimoto's thyroiditis) [60]. However, no study has previously evaluated night shift work and thyroid problems across different ethnicities. Our results show that white people working night shifts had a higher risk of hypothyroidism, due to increased TSH levels. They also had an increased risk of hyperthyroidism with higher tT3 and fT3 levels.

Those that work evening shifts also had an increased risk of hyperthyroidism, with elevated T3 and fT3 levels.

Black night shift workers had a higher risk of hyperthyroidism with decreased tT4 levels when compared to black daytime workers. Mexican-American evening workers, as with white people, had an increased risk of suffering from hypothyroidism compared to Mexican-American daytime workers, with increased TSH levels. They were equally more likely to suffer from autoimmune thyroiditis with increased ATG levels compared to Mexican-American daytime workers. These results might be due to white people being more at risk of suffering from thyroid diseases than black people, and as shown in Table 1, there is a majority of white people working night shifts.

9.4. Secondary analyses: Effect Modification by sleep

No study has yet analyzed night shift work and thyroid function across sleep duration or sleep problems. Our results showed that sleeping more than 8 hours and working nights is associated with higher risk of hypothyroidism and higher TSH levels. Evening workers with 7 hours sleep at night had a higher risk of presenting high TPO levels and those with less than 6 hours sleep had higher risk of hyperthyroidism with increased T3 levels. Our results showed that night shift workers and "another work schedule" workers with sleep problems had a higher risk of hyperthyroidism than daytime workers as they present increased T3 levels. People working another schedule and reporting sleep problems also presented higher chance of hyperthyroidism and decreased T4 levels compared to daytime workers with decreased T4 levels.

9.5. Sensitivity analysis

Sensitivity analysis was used to assess the influence of an unmeasured confounder on causal conclusion. We also used it to describe preclinical thyroid disease associated with shift work [61]. In the present study, history of thyroid disease and medication intake are variables that could have an impact on the causal link between night shift work and thyroid biomarkers. People with a medical background of, or current thyroid disease, in addition to those on

medication, were therefore excluded from this analysis. Our results show that people working evening shifts had a higher risk of presenting hypothyroidism (with increased TSH levels) than daytime workers, when adjusted for confounders. Night shift workers do not appear to be at a higher risk of thyroid disorders.

9.6. Strengths and Limitations

Our study has several limitations. First, information was collected via a self-administered questionnaire, which may lead to a social desirability bias, meaning that the answers given by the participants may be guided by their desire to please, to give a positive social image of themselves. This bias may be present, for example, in questions concerning certain lifestyle habits (smoking, alcohol…etc.). Also, self-reported data may lead to under- or over-reporting (e.g. of sleep duration). Additionally, some thyroid hormones follow a circadian rhythm and a lack of information about the time of sample collection may cause misleading results. Furthermore, diagnosed sleep disorders such as insomnia, restless leg syndrome, sleep apnea, were only available for the 2007-2008 cycle. If these variables had been present in the other cycles, a more thorough analysis would have been made concerning thyroid biomarkers and sleep quality. Another limitation is the fact that the night shift category only represents 4.76% of the whole work schedule variable, which means the power might have been limited to detect a statistically significant difference. This could explain why only a few significant results were found. An additional limitation is the study design. A cross-sectional study is an observational study, where outcomes and exposures are measured at the same time, just like a "snapshot" of a group of individuals. The limitations of cross-sectional studies include the difficulty of assessing a causal inference, or the inability to measure incidence. The results were not adjusted for multiple comparisons, and should be interpreted explanatorily only.

However, this study also has several strengths. To our knowledge, no other study has yet analyzed the association between five thyroid biomarkers and shift work schedule and sleep in a national US sample. Also, by combining three cycles, this study has a large sample size as well as access to a wide range of potential confounders.

X. Conclusion and perspectives

In conclusion, this study found that evening workers are at higher risk of hypothyroidism, with impacted T3 levels. Less conclusive results were found for night shift workers, although in some cases (when stratified for gender, ethnicity, and sleep), night workers exhibited significantly higher thyroid biomarkers than day workers. Sleep duration did not have any effect on thyroid biomarker levels, whereas people having sleep problems were more likely to suffer from hypothyroidism. Gender and ethnicity stratification showed clearly evidence that male and white people are more at risk of thyroid problems when working evening or night shifts. People working evening shifts are more likely to have ATG and TPO positivity. Sensitivity analysis showed that when excluding people having thyroid disease history or being on any kind of medication the risk of thyroid problems for people working evening shifts was even higher. Longitudinal studies are warranted to determine a causal link between night shift work and thyroid problems.

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XII. Appendix

12.1. Participant's questionnaire

OCQ.265 Which of the following best describes the hours {you/SP} **usually** {work/works} at {your/his/her} main job or business?

INTERVIEWER INSTRUCTION: IF THE RESPONDENT SAYS "FLEXTIME", ETC., PROBE TO DETERMINE WHETHER THE SHIFT THAT IS WORKED ACTUALLY FALLS IN A DAY, EVENING, NIGHT, OR ROTATING SHIFT CATEGORY BEFORE CODING IT AS "ANOTHER SCHEDULE."

A regular daytime schedule	1
A regular evening shift	2
A regular night shift	3
A rotating shift	4
Another schedule	5
REFUSED	7
DON'T KNOW	9

HELP SCREEN:
Standard Shift Definitions are:
A regular daytime schedule: this is work anytime between 6am and 6pm.
A regular evening shift: this is work anytime between 2pm and midnight.
A regular night shift: this is work anytime between 9pm and 8am.
A rotating shift: a work shift that changes periodically from days to evenings or nights.
Another schedule includes: a split shift (consisting of two distinct work periods each day), an irregular schedule arranged by the employer, or any other schedule.

OCQ.180 How many hours did {you/SP} work **last week** at **all** jobs or businesses?

|___|___|___|
ENTER NUMBER OF HOURS

CAPI INSTRUCTION:
HARD EDIT 1-168.

REFUSED	77777
DON'T KNOW	99999

BOX 1

CHECK ITEM OCQ.200:
IF HOURS IN OCQ.180 <= 34, OR REFUSED (CODE 777), OR DON'T KNOW (CODE 999), CONTINUE.
OTHERWISE, GO TO OCQ.220.

SLEEP DISORDERS – SLQ
Target Group: 16+

SLQ.010 H/M The next set of questions is about {your/SP's} sleeping habits.

How much sleep {do you/does SP} usually get at night on weekdays or workdays?

INTERVIEWER INSTRUCTION: IF RESPONDENT SLEEPS FOR ONLY VERY SHORT PERIODS OF TIME, ASK HIM/HER TO ESTIMATE ON AVERAGE THE TOTAL NUMBER OF HOURS THAT THEY GENERALLY SLEEP AT NIGHT.

|__|__|
ENTER HOURS

CAPI INSTRUCTION: HARD EDIT: HOURS MUST EQUAL 0-24.

REFUSED 777
DON'T KNOW 999

SLQ.050 {Have **you**/Has SP} **ever told** a doctor or other health professional that {you have/s/he has} trouble sleeping?

YES	1	
NO	2	
REFUSED	7	
DON'T KNOW	9	

SLQ.060 {Have **you**/Has SP} **ever been told** by a doctor or other health professional that {you have/s/he has} a sleep disorder?

YES	1	
NO	2	(SLQ.080)
REFUSED	7	(SLQ.080)
DON'T KNOW	9	(SLQ.080)

SMQ.040 {Do you/Does SP} **now** smoke cigarettes . . .

every day,	1	(SMQ.077)
some days, or	2	(SMQ.641)
not at all?	3	(SMQ.050Q/U)
REFUSED	7	(END OF SECTION)
DON'T KNOW	9	(END OF SECTION)

PAQ.705 Now I'd like to ask you some questions about {SP's} activities.

How many times per week does {SP} play or exercise enough to make {him/her} **sweat** and **breathe hard**?

IF NEVER, ENTER 0
IF LESS THAN ONCE PER WEEK, ENTER 1

|__|__|
ENTER NUMBER OF TIMES

REFUSED	77
DON'T KNOW	99

WEIGHT HISTORY – WHQ
Target Group: SPs 16+

WHQ.010 G/F/I/M/C

These next questions ask about {your/SP's} height and weight at different times in {your/his/her} life.

How tall {are you/is SP} without shoes?

ENTER HEIGHT IN FEET AND INCHES OR METERS AND CENTIMETERS

|__|__|
ENTER NUMBER OF FEET

AND

|__|__|
ENTER NUMBER OF INCHES

OR

|__|__|
ENTER NUMBER OF METERS

AND

|__|__|__|
ENTER NUMBER OF CENTIMETERS

OR

REFUSED 7777
DON'T KNOW 9999

ALQ.031

During the past 30 days, on how many days did you have at least one drink of alcohol?

INSTRUCTIONS TO SP:
Please select one of the following choices.

HARD EDIT: If (ALQ.022 = 2 and ALQ.031 in (3,4,5,6,7)) or (ALQ.022 =3 and ALQ.031 in (5,6,7)) or (ALQ.022 = 4 and ALQ.031 in (6,7)) then ERROR
Error message: "Your response is not consistent with your lifetime use. Please press the "Back" button, press "Clear," and try again."

0 days	1	(END OF SECTION)
1 or 2 days	2	
3 to 5 days	3	
6 to 9 days	4	
10 to 19 days	5	
20 to 29 days	6	
All 30 days	7	
REFUSED	77	
DON'T KNOW	99	

DMQ.141 What is the **highest** grade or level of school {you have/SP has} **completed** or the **highest degree** {you have/s/he has} **received**?

HAND CARD DMQ1
READ HAND CARD CATEGORIES IF NECESSARY.
ENTER HIGHEST LEVEL OF SCHOOL.

NEVER ATTENDED/KINDERGARTEN ONLY	0	(BOX 1B)
1ST GRADE	1	
2ND GRADE	2	
3RD GRADE	3	
4TH GRADE	4	
5TH GRADE	5	
6TH GRADE	6	
7TH GRADE	7	
8TH GRADE	8	
9TH GRADE	9	
10TH GRADE	10	
11TH GRADE	11	
12TH GRADE, NO DIPLOMA	12	
HIGH SCHOOL GRADUATE	13	
GED OR EQUIVALENT	14	
SOME COLLEGE, NO DEGREE	15	
ASSOCIATE DEGREE: OCCUPATIONAL, TECHNICAL, OR VOCATIONAL PROGRAM	16	
ASSOCIATE DEGREE: ACADEMIC PROGRAM	17	
BACHELOR'S DEGREE (EXAMPLE: BA, AB, BS, BBA)	18	
MASTER'S DEGREE (EXAMPLE: MA, MS, MEng, MEd, MBA)	19	
PROFESSIONAL SCHOOL DEGREE (EXAMPLE: MD, DDS, DVM, JD)	20	
DOCTORAL DEGREE (EXAMPLE: PhD, EdD)	21	
REFUSED	77	
DON'T KNOW	99	

DMQ.380 {Are you/Is SP} **now** married, widowed, divorced, separated, never married or living with a partner?

MARRIED	1	
WIDOWED	2	
DIVORCED	3	
SEPARATED	4	
NEVER MARRIED	5	(BOX 1D)
LIVING WITH PARTNER	6	
REFUSED	7	
DON'T KNOW	9	

DMQ.261 What race {do you/does SP} consider {yourself/himself/herself} to be? Please select 1 or more of these categories.

HAND CARD DMQ5
SELECT 1 OR MORE

WHITE	10	(BOX 4)
BLACK/AFRICAN AMERICAN	11	(BOX 4)
INDIAN (AMERICAN)	12	(BOX 4)
ALASKA NATIVE	13	(BOX 4)
NATIVE HAWAIIAN	14	(BOX 4)
GUAMANIAN	15	(BOX 4)
SAMOAN	16	(BOX 4)
OTHER PACIFIC ISLANDER (SPECIFY)	17	(BOX 4)
ASIAN INDIAN (INCLUDES PERSONS OF INDIA, PAKISTAN, CEYLON, AND SRI LANKA)	18	(BOX 4)
CHINESE	19	(BOX 4)
FILIPINO (FROM PHILIPPINES)	20	(BOX 4)
JAPANESE	21	(BOX 4)
KOREAN	22	(BOX 4)
VIETNAMESE	23	(BOX 4)
OTHER ASIAN	24	(DMQ.264)
SOME OTHER RACE	25	(DMQ.267)
REFUSED	77	(BOX 4)
DON'T KNOW	99	(BOX 4)

CAPI INSTRUCTION:
THE WORDS "INDIA", "PAKISTAN", "CEYLON", AND "SRI LANKA" SHOULD APPEAR IN BLUE.

INQ.235 What is the total income received last month, {LAST CALENDAR MONTH & CURRENT CALENDAR YEAR} by {you/NAMES OF OTHER FAMILY/you and NAMES OF FAMILY MEMBERS}} before taxes?

[Please include income from all sources we have just talked about such as wages, salaries, Social Security or retirement benefits, help from relatives and so forth.]

[INTERVIEWER INSTRUCTION: IF SP DOES NOT KNOW INCOME OF OTHER FAMILY MEMBERS, ENTER DON'T KNOW.]

CAPI INSTRUCTION:
- REQUIRE DOUBLE ENTRY OF INCOME.
- SCREEN SHOULD READ:
  "LAST MONTH'S INCOME FOR {NAMES OF FAMILY MEMBERS} HAS BEEN RECORDED AS {INCOME ENTERED IN INQ.200} DOUBLE ENTRY OF INCOME REQUIRED."
- IF ENTRIES DO NOT MATCH, DISPLAY BOTH ENTRIES. INTERVIEW SHOULD SELECT ENTRY TO CORRECT.
- FOR THE CALENDAR FILL: IF CURRENT MONTH IS JANUARY THE PAST CALENDAR YEAR WILL BE SHOWN

$ |___|___|___|___|___|___|___|___|___| (BOX NEW 7A)

REFUSED	7
DON'T KNOW	9

DMQ.267 CODE SP ANSWER TO 'OTHER RACE'.

MEXICAN	1
PUERTO RICAN	2
CUBAN	3
DOMINICAN REPUBLIC	4
CENTRAL AMERICAN:	
COSTA RICAN	5
GUATEMALAN	6
HONDURAN	7
NICARAGUAN	8
PANAMANIAN	9
SALVADORAN	10
OTHER CENTRAL AMERICAN	11
SOUTH AMERICAN:	
ARGENTINEAN	12
BOLIVIAN	13
CHILEAN	14
COLOMBIAN	15
ECUADORIAN	16
PARAGUAYAN	17
PERUVIAN	18
URUGUAYAN	19
VENEZUELAN	20
OTHER SOUTH AMERICAN	21
OTHER HISPANIC OR LATINO:	
SPANIARD	22
SPANISH	23
SPANISH AMERICAN	24
HISPANIC/LATINO	25
HISPANO/HISPANA	26
OTHER SPECIFY	40
REFUSED	77
DON'T KNOW	99

m.	had a thyroid (thigh-roid) problem? YES 1 → NO 2 (k) REFUSED 7 (k) DON'T KNOW 9 (k)	have a thyroid problem? YES 1 NO 2 REFUSED 7 DON'T KNOW 9	had a thyroid problem? |___|___|___| ENTER AGE IN YEARS REFUSED 777 DON'T KNOW 999

RXQ.032 In the **past 30 days**, {have you/has SP} used or taken medication for which a **prescription** is needed? Include only those products prescribed by a health professional such as a doctor or dentist. [Do not include prescription vitamins or minerals you may have already told me about.]

YES	1
NO	2
REFUSED	7
DON'T KNOW	9

12.2. Consent form

FORM APPROVED: OMB # 0920-0237

NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (NHANES)
CONSENT/ASSENT AND PARENTAL PERMISSION FOR SPECIMEN STORAGE AND CONTINUING STUDIES

Print name of participant _____
First Middle Last

Q **Why will a sample of blood and urine be kept for future health studies?**

A We would like to store some of the urine, blood, and saliva from persons who are examined in NHANES for future health studies. These samples will be frozen and kept in a specimen bank for as long as they last.

Q **What studies will be done with the samples?**

A At this time, no specific studies are planned besides the tests included in the NHANES exam. As scientists learn more about health and diseases, other studies will be conducted that may include stored samples. People conducting these studies will not contact NHANES participants for any additional information.

We will keep strictly private all health data and samples that we collect in NHANES. Our staff is not allowed to discuss that any person is part of this survey under penalty of Federal laws: Section 308(d) of the Public Health Service Act (42 USC 242m) and the Privacy Act of 1974 (5 USC 552A).

Q **Who can use the stored samples for further study?**

A Researchers from Federal agencies, universities, and other scientific centers can submit proposals to use the stored specimens. These proposals will be reviewed for scientific merit and by a board that determines if the study proposed is ethical. The NHANES program will always know which samples belong to you or your child, but we will not give other researchers any information that could identify you or your child.

Q **Will I receive results from any future testing of my specimens?**

A Most studies will simply add to our knowledge of health and disease. Therefore, we do not plan to contact you or your family with individual results from these studies. Periodically we will send a newsletter telling all NHANES participants about the studies being conducted. To get more general information about a particular study, you can call our toll-free number, 1-800 452-6115.

Q **What genetic studies will be done and what part will my DNA sample play?**
(DNA samples will be collected only on those ages 20 or over.)

A Genetic studies look at the DNA found in cells. We will store part of the blood and saliva sample that we collect in the exam center for future genetic studies. We will keep this material for an unlimited time. Studies of human genes are helping us learn about many diseases and health conditions. The information from people who are part of NHANES could help that effort.

If you wish to have your samples used for future genetic studies, you will have a chance to say so when you sign this consent form.

Q **How can I remove blood, urine, or saliva samples from the specimen bank?**

A In the future, if you want samples removed from the specimen bank, call us toll-free at 1-800 452-6115.

The results of continuing study of your stored specimens may help find new ways to prevent, treat, and cure many diseases.

For **persons ages 7 and over,** check this box
❑ I agree that my blood, urine, and saliva (if applicable) may be kept for future health studies

For **parent/guardian of a child under the age of 18**, check this box
❑ I agree that my child's blood and urine may be kept for future health studies

Genetic testing studies may be done with DNA samples collected only on those **ages 20 or over.** If you wish to have your samples used for future genetic studies, check the box below:

Only for **persons ages 20 and over**, check this box
❑ I agree that my blood and saliva may be kept for future studies using my genes to help understand genetic links to medical conditions.

_____ _____
Signature of participant age 7 or over Date

_____ _____
Signature of parent/guardian of participant under 18 Date

_____ _____ _____ _____
Signature of staff member Date Witness (if required) Date

_____
SP ID

12.3. NHANES Ethics Approval

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives. Protecting People.™

NCHS Research Ethics Review Board (ERB) Approval*

Survey Name/Date	NCHS IRB/ERB Protocol Number or Description
NHANES 2013-2014	Continuation of Protocol #2011-17
NHANES 2011-2012	Protocol #2011-17
NHANES 2009-2010	Continuation of Protocol #2005-06
NHANES 2007-2008	Continuation of Protocol #2005-06
NHANES 2005-2006	Protocol #2005-06
NHANES 1999-2004	Protocol #98-12
NHANES III	Institutional Review Board (IRB) approval and documented consent was obtained from participants
NHANES II	Underwent internal human subjects review, but IRB approval using current standards was not obtained.
NHANES I	Underwent internal human subjects review, but IRB approval using current standards was not obtained.
NHES	Underwent internal human subjects review, but IRB approval using current standards was not obtained.

* In 2003, the NHANES Institutional Review Board (IRB) changed its name to the NCHS Research Ethics Review Board (ERB).

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12.4. Request to the University of Liège Ethics Committee

Demande d'avis au Comité d'Ethique dans le cadre des mémoires des étudiants du Master en Sciences de la Santé publique

(***Version finale acceptée par le Comité d'Ethique en date du 06 octobre 2016)***

mssp@uliege.be.

thique a déjà été obtenu concernant le projet de recherche, merci de

s reçu au présent formulaire.

1. Etudiant·e (prénom, nom, adresse courriel) : Damas Kira-Kibibe

2. Finalité spécialisée : EPES 3. Année académique : 2021-2022

4. Titre du mémoire : Shift work and biomarkers of thyroid function in the National Health and Nutrition Examination Survey (2007-

5. Nom du Service ou nom du Département dont dépend la réalisation du mémoire : Medical University of Vienna, Public Health Center, Department of Epidemiology.

6. Nom du/de la Professeur·e responsable du Service énoncé ci-dessus ou nom du/de la Président·e de Département : Eva Schernhammer

7. Promoteur·trice·s (titre, prénom, nom, fonction, adresse courriel, institution) :

a. Kyriaki Papantoniou

b. Lin Yang

8

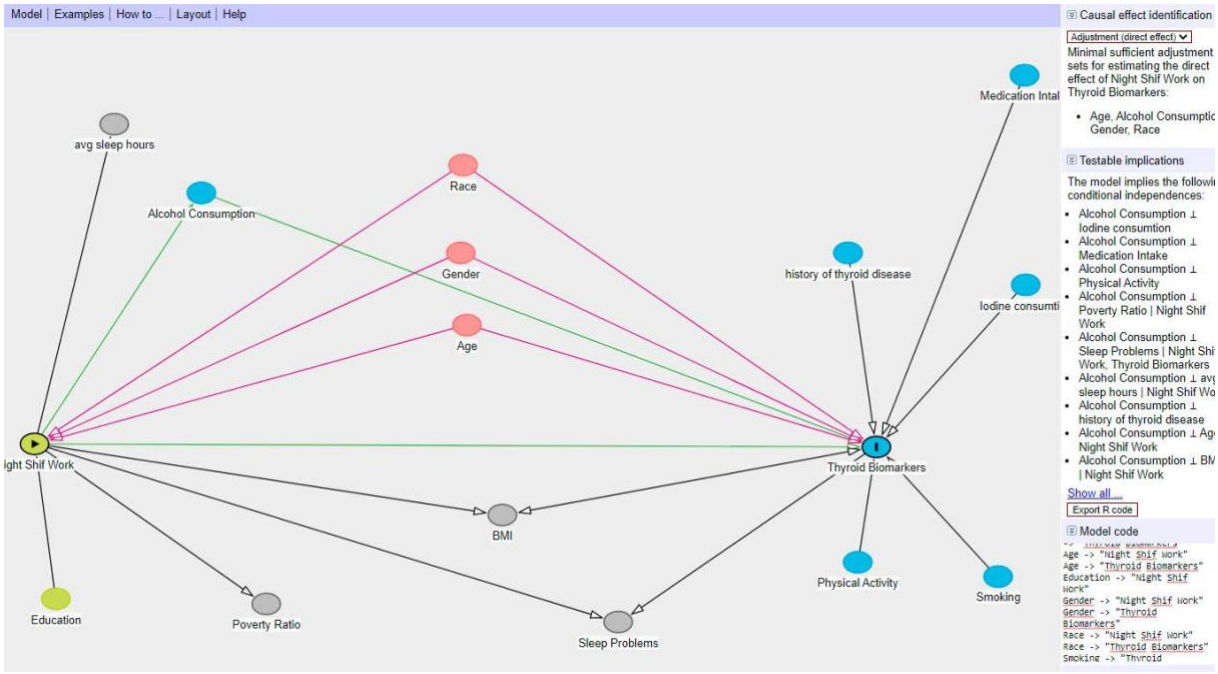
a. Objectifs

xaminer l'association entre le travail de nuit, le sommeil et les biomarqueurs de la fonction thyroïdienne dans la base de données NHANES durant trois cycles : de 2007 à 2008, de 2009 à 2010 et de 2011 à 2012.

b. Protocole de recherche (design, sujets, instruments, etc.) (**+/- 500 mots**)

Le design d'étude est transversale. Cette étude va exploiter certaines variables de la base de données « National Health and Nutrition Examination Survey » (NHANES) obtenues sur 3 cycles consécutifs (2007-2008, 2009-2010 et 2001-2012). Cette base de données est destinée à représenter la totalité de la population civile américaine non institutionnalisée résidant dans les 50 États américains tionnage en quatre étapes. Chaque année, un échantillon représentatif est sélectionné et chaque participant signe un

12.5. Dag code



12.6. Unadjusted Regression Models

Table 1. Linear Regression of thyroid biomarkers and work schedule

Ref = Daytime	**Evening**	**Night**	**Rotating**	**Another**
	β (95%CI)	*β (95%CI)*	*β (95%CI)*	*β (95%CI)*
TSH (µIU/mL)	0.21 (-0.09,0.51)	0.17 (-0.18,0.52)	-0.09 (-0.35,0.17)	0.07 (-0.20,0.35)
ATG (IU/mL)	0.01 (-0.02,0.22)	-0.01 (-0.16,0.13)	-0.01 (-0.12,0.10)	0.02 (-0.01,0.14)
TPO (IU/mL)	0.09 (-0.14,0.31)	-0.11 (-0.37,0.15)	-0.06 (-0.26,0.13)	0.04 (-0.17,0.25)
tT3 (ng/dL)	3.58 (0.17,7.00)	4.45 (0.44,8.46)	3.56 (0.58,6.55)	-0.42 (-3.62,2.77)
tT4 (ug/dL)	-0.13 (-0.33,0.07)	-0.13 (-0.37,0.11)	0.03 (-0.14,0.21)	-0.11 (-0.30,0.08)
fT3 (pg/mL)	0.08 (-0.01,0.17)	0.08 (-0.02,0.18)	0.03 (-0.05,0.11)	-0.03 (-0.11,0.05)
fT4 (ng/dL)	-0.01 (-0.03,0.02)	-0.02 (-0.05,0.01)	-0.01 (-0.03,0.01)	-0.00 (-0.02,0.02)

There is no significant difference between TSH, ATG, TPO, TT4, T3F and T4F levels among night shift workers compared to daytime workers, but total T3 levels are significantly different across work schedules. Evening workers have an increase of 3.58 ng/dL (IC: 0.17,7.00) in their tT3 levels compared to daytime worker, night shift workers have an increase of 4.45 nd/dL (IC: 0.44,8.46) in their tT3 levels compared to day workers and rotating schedule workers have an increase of 3.56 ng/dL (IC: 0.58,6.55) in their tT3 levels compared to day workers.

Table 2. Association between thyroid biomarker levels and sleep duration.

Ref = regular sleep	**Short sleep**	**Long sleep**
	β (95%CI)	*β (95%CI)*
TSH (µIU/mL)	-0.12 (-0.30,0.05)	0.03 (-0.15,0.23)
ATG (IU/mL)	-0.06 (-0.13,0.02)	-0.07 (-0.15,0.01)
TPO (IU/mL)	-0.08 (-0.21,0.05)	-0.07 (-0.22,0.07)
tT3 (ng/dL)	0.32 (-1.70,2.33)	1.56 (-0.62,3.75)
tT4 (ug/dL)	-0.02 (-0.14,0.10)	0.04 (-0.09,0.17)
fT3 (pg/mL)	0.03 (-0.02,0.08)	0.01 (-0.05,0.07)
fT4 (ng/dL)	-0.01 (-0.02,0.00)	0.00 (-0.01,0.01)

Note: short sleep (<6 hours of sleep per night), regular sleep (7 hours sleep per night), long sleep (>8 hours sleep per night).

There is no significant difference in thyroid levels across short or long sleep.

Table 3. Average thyroid biomarker levels according to self-reported sleep problems

Ref = No	**Sleep problems**	**Sleep disorder**
	β (95%CI)	*β (95%CI)*
TSH (µIU/mL)	0.13 (-0.06, 0.32)	0.08 (-0.23, 0.39)
ATG (IU/mL)	-0.03 (-0.10, 0.05)	-0.04 (-0.17, 0.09)
TPO (IU/mL)	0.08 (-0.06, 0.22)	-0.04 (-0.28, 0.19)
tT3 (ng/dL)	-3.90 (-6.07, 1.73)	-5.21 (-8.83, -1.58)
tT4 (ug/dL)	-0.10 (-0.23, 0.03)	-0.07 (-0.29, 0.14)
fT3 (pg/mL)	-0.13 (-0.19, -0.08)	-0.11 (-0.21, -0.02)
fT4 (ng/dL)	-0.01 (-0.03, 0.00)	0.00 (-0.02, 0.03)

People with sleep problems have significantly a decrease of 0.13 pg/mL (95%CI: -0.13,- 0.08) in their fT3 levels compared to people not suffering from sleep problems.

12.7. Log transformation from ATG and TPO

Every significant beta coefficient and interval confidence is going to be transformed to get a percentage used to analysis of the regressions.

12.7.1. Biomarkers and work schedule

ATG

- Model 1, evening shift: (exp(0.14)-1)*100 IC : (exp(0.02)-1)*100 and (exp(0.27)-1)*100
- Model 2, evening shift: (exp(0.24)-1)*100 IC : (exp(0.08)-1)*100 and (exp(0.39)-1)*100
- Model 3, evening shift: (exp(0.22)-1)*100 IC : (exp(0.06)-1)*100 and (exp(0.38)-1)*100

12.7.3. Effect Modification by gender

ATG

- Female, evening shift: (exp(0.27)-1)*100 IC : (exp(0.06)-1)*100 and (exp(0.47)-1)*100

TPO

- Male, night shift: (exp(-0.36)-1)*100 IC : (exp(-0.65)-1)*100 and (exp(-0.06)-1)*100
- Female, evening shift: (exp(4.36)-1)*100 IC : (exp(0.81)-1)*100 and (exp(7.90)-1)*100

12.7.4. Effect Modification by ethnicity

ATG

- Mexican-American, evening shift: (exp(0.32)-1)*100 IC : (exp(0.02)-1)*100 and (exp(0.63)-1)*100

12.7.5. Effect Modification by sleep

TPO

- Regular sleep, evening shift: (exp(0.46)-1)*100 IC : (exp(0.02)-1)*100 and (exp(0.65)-1)*100

12.7.6. Sensitivity Analysis

ATG

- Model 3, evening shift: (exp(0.22)-1)*100 IC : (exp(0.06)-1)*100 and (exp(0.38)-1)*100

TPO

- Model 2, night shift: (exp(0.35)-1)*100 IC : (exp(0.01)-1)*100 and (exp(0.69)-1)*100