URANIUM EXPOSURE AND AUTOIMMUNE THYROID DISEASE IN POPULATIONS NEAR THE FERNALD FEED MATERIALS PRODUCTION CENTER

By

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A Thesis

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CERTIFICATE OF APPROVAL

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GLOSSARY OF TERMS AND ACRONYMS

(Adapted from Killough et. al, 1998b)[1]

AITD: Autoimmune Thyroid Disease.

Antigen-presenting cells: Specialized white blood cells that identify and fight antigens that enter the body.

ATSDR: Agency for Toxic Substances and Disease Registry. Evaluated past airborne uranium exposures from the FMPC and evaluated whether the exposure had the potential to cause adverse health outcomes among participants in the FMMP.

Background radiation: The amount of ionizing radiation to which a person is exposed from natural sources, such as radiation from naturally occurring radionuclides in the soil, or cosmic radiation originating in outer space. Exposure from natural sources, on average, is about 3.1mSv per year.[2]

CDC: Centers for Disease Control and Prevention. Funded the Fernald Dosimetry Reconstruction Project, is part of the U.S. Department of Health and Human Services.

Curie: A unit of ionizing radiation approximately equivalent to the amount of radioactivity emitted by one gram of radium-226.[3]

Depleted uranium: Result of the removal of 235U and 234U, so that the proportion of 238U is increased. It can be compared to natural and enriched uranium. At the FMPC, depleted uranium typically contained 0.14-0.20% uranium-235.

Direct radiation exposure: Refers to one pathway of exposure of people to radiation from the FMPC. In this exposure pathway, penetrating radiation emitted from radioactive material is partially absorbed by individuals exposed to it. The amount of exposure decreases with distance from the source. An example is gamma radiation from the K-65 silos that resulted in low-level exposure of nearby residents.

DOE: U.S. Department of Energy.

Dose: A general term denoting the quantity of radiation or energy that is absorbed by the body.

Dose Reconstruction: A scientific study that estimates doses to people from releases of radioactivity or other contaminants into the environment from a facility.

Effective dose: Provides a measure of the dose to the whole body, taking into account the dose absorbed by each of the target organs and the sensitivity of those organs to radiation. The unit of effective dose is Sievert (Sv).

Enriched uranium: Result of an increase in 234U. It can be compared to natural and depleted uranium. At the FMPC, enriched uranium typically contained 0.95-1.25% uranium-235. While most of the enriched uranium at the FMPC was in the above range, some processing of 2% enriched uranium occurred in the 1960s. The capability to digest 5% enriched uranium was added to Plant 1 in 1970.

EPA: U.S. Environmental Protection Agency

Exposure pathways: Ways in which people are exposed to contaminants in the environment. The key exposure pathways are air and water, with most exposures occurring by inhalation, drinking water, ingestion of locally-grown cultivated crops and animal products and other foods, and from direct irradiation.

FMMP: Fernald Residential Medical Monitoring Program

FMPC: Feed Materials Production Center. The name of the site until 1991.

FT4: Free Thyroxine (T4). T4 that is not bound to target tissues or transport proteins. Those with hyperthyroidism will have elevated FT4.

Graves' Disease: Occurs when autoantibodies (Anti-TSHR) bind to the TSH receptor and stimulate it, causing overproduction of the thyroid hormone which leads to *hyperthyroidism*. It is characterized by elevated Thyroxine (T3 and T4), low TSH, and presence of Anti-TSHR.

Hashimoto Thyroiditis: Occurs when inflammation caused by an autoimmune process destroys the thyroid gland, leading to an insufficient production of thyroid hormones (T3 and T4) leading to *hypothyroidism*. Diagnosis is normal FT4 but elevated TSH OR low FT4 and T3 but elevated TSH, and possible goiter. Can lead to development of a goiter, weight gain, and sometimes, thyroid cancer.

Idiopathic Myxedema: Also known as complete hypothyroidism, it has been used as a marker for AITD in other studies. It is characterized as atrophic thyroid gland, with positive auto-antibodies including TSH-stimulation blocking antibody (TSBAb). Idiopathic Myxedema is the end stage of a lymphocytic thyroiditis in which humoral and cellular autoimmune processes lead to failure of the thyroid function. It is a less specific autoimmune thyroid disease outcome, as it is not either Graves' or Hashimoto's disease, but may capture patients who were diagnosed with hypothyroidism prior to or after developed of Graves' or Hashimoto's disease.

ICD-9 : International Statistical Classification of Diseases and Related Health Problems using a numeral system for the standardized classification of health outcomes.

Ionizing radiation: A type of radiation that has enough energy to create ions (ionized atoms that are chemically active) inside living cells. These ions can damage key substances in cells, including the DNA within the cell nucleus. Such damage can lead to cancer or other defects.

K-65 silos: Large concrete tank-like structures that store residues from the extraction of uranium from ores that were processed during the early years of FMPC operations.

Natural uranium: Made of three isotopes (238U, 235U, and 234U). It can be compared with enriched and depleted uranium. Natural or "normal" uranium contains 0.72% uranium-235.

NHANES: National Health and Nutrition Examination Survey. "A program of studies designed to assess the health and nutritional status of adults and children in the United States. The survey is unique in that it combines interviews and physical examinations."[4]

NLO: National Lead Company of Ohio, the contractor for the FMPC through the end of 1985.

RAC: Radiological Assessments Corporation. The organization contracted by CDC to conduct the Fernald Dosimetry Reconstruction Project.

Radionuclide: A radioactive element, for example uranium-238 or radon-222.

Radium: A naturally occurring, radioactive metallic substance that occurs most commonly as an isotope with an atomic weight of 226 (radium-226). It occurs in minute quantities associated with uranium in natural ores.

Radon: A radioactive, nonreactive gas. There are three isotopes of radon that occur in nature as members of the actinium, thorium, and uranium series. Most human exposure to radon is from uranium naturally present in soil and rock. The gas is created and leaves the soil as the uranium-238 decays through several products to radium-226, then on to radon-222 gas. Radon and its own decay products (radioactive particles created as radon decays) may then be inhaled by humans.

Radon-222: A naturally occurring decay product of uranium**.** At Fernald, radon-222 has been released from the onsite storage of K-65 material, a waste from the processing of uranium ore. This material, stored in two large silos onsite, contains high concentrations of radium-226 and, thus, acts as a continuous source of radon-222.

Sievert (Sv): The unit of ionizing radiation dose. Measure of the amount of energy delivered to a target tissue or organ.

T3: Triiodothyronine. Hormone released from the thyroid when stimulated by TSH. It assists in metabolic function. Grave's disease is characterized by elevated T3 while Hashimoto Thyroiditis is characterized by insufficient T3.

T4: Thyroxine. Hormone released from the thyroid when stimulated by TSH. Grave's disease is characterized by elevated T4 while Hashimoto's is characterized by insufficient T4.

Tg: Thyroglobulin: A major autoantigen in Hashimoto's disease.

TPO: Thyroid peroxidase: A major autoantigen in Hashimoto's disease.

TSH: Thyroid-stimulating hormone. TSH produces triiodothyronine (T3) and thyroxine (T4) which help with metabolism function.[5] Graves' Disease is characterized by low TSH while Hashitomo's Thyoriditis is characterized by elevated TSH.

TSHR: Thyroid-stimulating hormone receptor antibodies. The major autoantigen in Graves' disease.

TSBAb: TSH-stimulation blocking antibody. Causes hypothyroidism.

T-cells: A type of lymphocyte that controls immune responses and is often dysfunctional in AITD patients.[6]

µg/L: Micrograms per liter (urine or blood).

ug/m^3: Micrograms per meter cubed. Unit used for cumulative airborne uranium exposure estimates.

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The completion of this thesis would not have been possible without the support and guidance from several key individuals.

Foremost, I wish to thank Dr. Susan M. Pinney for allowing me the incredibly rewarding opportunity to work with the Fernald Residential Medical Monitoring (FMMP) Database. It is she who originally suggested that I examine Autoimmune Thyroid Disease as an adverse health outcome in the Fernald population. Dr. Pinney has made herself available for my many, many questions and has served as an invaluable source of knowledge on the history of the Fernald Feed Material Production Center, the FMMP cohort, and environmental exposure estimates. I consider myself extremely lucky to have had such an accomplished and supportive mentor for my thesis.

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Abstract

Background. From 1951 to 1989, the Fernald Feed Materials Production Center released uranium dust into the atmosphere and ground water, resulting in contamination of the surrounding rural area. Residents expressed multiple health concerns, one of which was thyroid health. Little research has examined the effects of uranium exposure and autoimmune thyroid disease (AITD) in the general population. The Fernald Resident Medical Monitoring Program (FMMP) provides a unique opportunity to examine the presence of AITD among a cohort of adults with individually estimated airborne uranium exposure.

Purpose. To evaluate the association between uranium exposure and AITD. Demonstration of an association would alert FMMP physicians to be especially aware of thyroid health among participants who live or have lived in the Fernald area leading to early detection and treatment.

Methods. ICD-9 codes assigned to disease conditions over the 18-year follow-up on 8,787 adult FMMP participants were used to identify cases of AITD. Cases were frequency matched by year of birth and sex to create a 1:4 case-control ratio. Identified incident cases were categorized into four AITD outcomes, all AITD Cases and three subcategories: a) Hashimoto Thyroiditis (ICD-9: 245.2), b) Graves' Disease (ICD-9: 242.0), and c) Idiopathic Myxedema (ICD-9: 244.9). Cumulative airborne uranium exposure groups (low <0.25 ug/m^3; moderate=0.25-0.50 ug/m^3; high>0.50 ug/m^3) were created by FMMP investigators based on the individual continuous cumulative exposure estimates established through the efforts of the CDC Fernald Dosimetry Reconstruction Project. Multivariate logistic regression was used to examine the odds of exposure type for each of the case outcome categorizations, adjusting for covariates.

Results. Cumulative airborne uranium exposure was not found to be associated with any of the AITD categories.

Conclusion. We failed to demonstrate an association between cumulative airborne uranium exposure and any of the AITD categories, in the FMMP population. While the community should be made known of the limitations of this study, based on our results, we suggest that AITD is not a top concern for the exposed residential population around Fernald. We believe that standard AITD screening and treatment procedures are sufficient for this population.

Chapter 1 - Introduction

Although uranium exposure has been linked to histopathological changes in the thyroid and to autoimmune thyroiditis, little research has examined the effects of uranium exposure and autoimmune thyroid disease in the general population.[8,9] The Fernald Resident Medical Monitoring Program (FMMP) provides a unique opportunity to examine the association of autoimmune thyroid disease (AITD) among adults with individual estimates of airborne uranium exposure (ug/m^3) created by the CDC Fernald Dosimetry Reconstruction Project.

The Source of Uranium Exposure

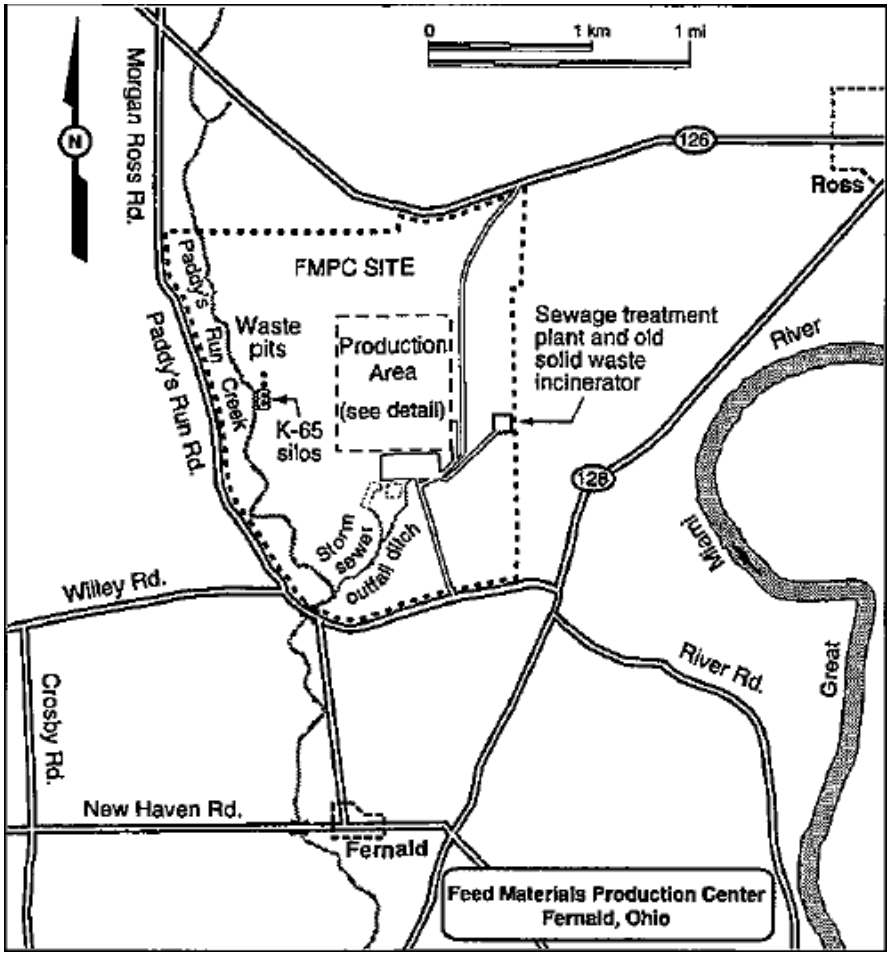
The Feed Materials Production Center (FMPC), located in rural Ohio, seventeen miles northwest of Cincinnati, became an important part of American national defense history when it was built as the initial uranium processing facility that supplied refined uranium to other facilities in the weapons complex during the Cold War.[10] This 1,050 acre site was a prime location for a 3 million dollar uranium purifying plant as it was located in a rural agricultural area which had access to "a skilled labor force (machinists); lower property values; a plentiful water supply; a nearby railroad line" and had "close proximity to Cincinnati and level terrain" (Figure 1).[10]

From 1951 to the end of 1989, the U.S. Department of Energy (DOE) and the U.S. Atomic Energy Commission supervised the conversion of uranium feed materials into uranium metal to be used as fuel cores for nuclear reactors at other DOE nuclear weapons centers.[11] For example, the refined uranium was used "as targets inserted into nuclear reactors at the Hanford facility in Washington state that produced plutonium for extraction and use in weapon construction".[7] During its production years, the FMPC produced approximately 500 million pounds of purified uranium metal, "67 percent of all the uranium used in the nation's cold war nuclear weapons program".[7,12]

The FMPC also provided radioactive and other hazardous waste storage and disposal, not only for waste generated at the site, but also for waste shipped in from other DOE facilities.[11] When the plant discontinued production in 1989, the site contained " 6.4 million cubic feet of containerized low-level waste; 186,000 gallons of low-level liquid mixed waste; 31million net pounds of nuclear product; 255 process-related and administrative structures; three concrete silos containing 13,990 cubic yards of low-level radioactive waste; six waste pits

containing more than 1 million tons of waste; 400 acres containing 2.4 million cubic yards of contaminated soil, and approximately 223 acres of a contamination plume in the sole-source aquifer beneath the site".[13]

Figure 1. Layout of the FMPC[1]



A Concerned Population

For nearly 30 years, the FMPC quietly operated in the center of a rural residential area. Prior to the class action suit filed by the citizens against National Lead of Ohio Inc in 1985, the true operations at the FMPC are thought to have been intentionally disguised. In an interview, Stan Chesley, the lawyer working on behalf of Fernald residents, stated that many residents thought the FMPC was part of Ralston Purina or a plant for making animal feed due to the red and white "checkerboard chimneys" on site.[14] In addition, the plant provided employment to many people who resided near the plant, and employees were instructed to keep plant operations private.[10] A final factor thought to be contributory to the DOE's ability to operate the plant for so long, so near a residential community, is the Cold War zeitgeist: the fear that contradicting weapon manufacturing efforts would appear anti-American or conspiratory.[14]

In the mid-1980's, however, citizens became aware of the environmental contamination resulting from the operations at the FMPC. In 1990, the Fernald Resident Medical Monitoring Program (FMMP) surveillance activities began as part of the 78 million dollar litigation settlement between the U.S. DOE and the citizens who resided around the facility.[11] The FMMP's mission was to "identify disease if present or to reassure those found to be healthy" in order to reduce emotional distress and to address the community concern that residents had been exposed to both radiologic and non-radiologic contaminants.[11]

The Feed Materials Production Center's legacy is best described by the Office of Legacy Management, a branch of the DOE responsible for managing activities for closed weaponry facilities: "What was once considered a patriotic mission for the nation's security would decades later be called threatening and dangerous operations".[10]

Figure 2. FMPC timeline of events (adapted from EPA[7])

1951: U.S. Atomic Energy Commission acquires property and builds facility.

1952: Uranium processing begins.

1984: Under EPA superfund requirements, site announces uranium release to the community.

1986: State of Ohio initiates claim against the DOE for violations of multiple environmental regulations; the EPA and DOE sign Federal Facilities Compliance Agreement initiating the Remedial Investigation/Feasibility Study.

1989: Site listed on the EPA's National Priorities List.

1989: Uranium production ceases.

1991: Mission officially changed to remediation.

1993-1996: Records of Decision issued for site's five operable units.

1998: The DOE issues draft Natural Resources Restoration Plan.

2006: Remedial actions complete with long-term ground water remedy in place; restoration projects under way.

2008: Fernald Preserve is open to the public.

Exposure Concerns Confirmed

The exposure concerns of the public were validated through efforts of the Centers for Disease Control and Prevention (CDC), the Radiological Assessments Corporation for dosimetry reconstruction, The Agency for Toxic Substances and Disease Registry **(**ATSDR**)**, and FMMP investigators. In 1990, after the plant ceased production, the CDC and the Radiological Assessments Corporation for dosimetry reconstruction assessed the magnitude of radiation and uranium exposure of residents around the FMPC and established estimates of past uranium exposure based on current and past DOE off-site environmental sampling data, soil samples, and private well and cistern samples.[15] This established the FMPC as a source of chemical and radioactive contamination, and estimated that between 1952 and 1989, 470,000 kilograms of uranium dust and 160,000 curies of radon^{222} were released into the atmosphere.[1]

During its production years, as a result of the chemical separation process, the FMPC released several chemical forms of uranium into the environment including uranium trioxide, uranium tetrafluoride, uranium hexafluoride, and uranyl nitrate.[16] Airborne releases included mostly semi-soluble uranium trioxide, uranium tetrafluoride, and uranium hexafluoride and primarily occurred before 1973.[16,17] Of note, the exposures from the FMPC were very different from the exposures released from the Hanford Plutonium Production Site in Washington State as radioactive I^{131}, released from Hanford, has the tendency to accumulate in the thyroid gland, while uranium particulate matter, released from the FMPC, tends to be associated with renal dysfunction.[18,19]

ATSDR scientists evaluated whether past airborne uranium exposures from the FMPC had the potential to cause adverse health outcomes among community members. ATSDR scientists estimated that the airborne uranium concentration in 1955 ($3.7x10^{-3}$ mg/m^3) was lower than the health based guideline ($8x10^{-3}$ mg/m^3) for inhalation of insoluble uranium, which made up the majority of airborne releases from the FMPC.[15] While airborne uranium exposure by itself may not be a health concern, a combination of uranium airborne exposure with exposure from other pathways was identified as a health concern by ATSDR scientists.[15]

Radon was also released into the environment, from radioactive waste storage silos on the FMPC site, until 1979 when the silos were finally sealed.[16,17] The CDC Fernald Dosimetry Reconstruction Project calculated cumulative lifetime whole body radiation dose equivalencies for nine hypothetical residents with differing ages, and distances and directions from the FMPC based on “particulate size and deposition, prevalent wind direction,

ground to air resuspension, flow parameters in surface and groundwater, and irrigation of crops.[17] For example, the scenario with the highest radiation does equivalent was a woman, living 1.7 km northeast of the FMPC for the entirely of plant operation, but not consuming well water. Her cumulative lifetime effective whole body radiation dose equivalent, above background level, was 61mSv.[17]

Two main exposure pathways were identified: 1) *inhalatio*n of airborne uranium, resulting from releases from dust collectors, scrubbers, waste incinerators, burn pads, waste pits, waste silos, and waste processing operations, as well as direct radiation from two waste silos; and 2) *ingestion* of uranium from consuming water from privately owned wells and cisterns.[15]

Addressing Health Concerns

Initially public health concerns were focused on cancer, but early research suggests that other health outcomes may also be important to examine. Pinney et al. (2003) reported an elevated prevalence of several other adverse health outcomes among FMMP participants, at enrollment, compared to national prevalence.[20] Specifically, at the time of the report, thyroid disease rates were higher in the FMMP population than national comparisons (Standardized Prevalence Ratio of thyroid diseases (FMMP vs NHIS): 1.55 (95% CI, 1.33-1.79)).[20] Even though not specifically examined by Pinney et.al (2003), community concerns about autoimmune thyroid disease have arisen.

Autoimmune disorders occur when the immune system incorrectly identifies healthy tissue as a threat and attacks and destroys itself.[21] Autoimmune thyroid disease (AITD) is characterized by "lymphocytic infiltration of the thyroid with autoantibodies targeting thyroid antigens, including thyroid peroxidase (TPO), thyroglobulin (Tg), or the thyroid stimulating hormone receptor (TSHR)".[22] Morbidity, as opposed to early mortality, is the primary issue of concern with this class of thyroid disease. In fact, those with a diagnosis of an AITD have an increased risk for having other autoimmune conditions, such as rheumatoid arthritis.[23] Women are affected by AITD more often than men, and most frequently between the ages of 20 and 40.[24]

There are two types of AITD. The first is Graves' Disease in which autoantibodies (Anti-TSHR) bind to the TSH receptor and stimulate it, causing overproduction of the thyroid hormones, T3 and T4, which leads to *hyperthyroidism*. It is characterized by elevated Thyroxine (T3 and T4), low TSH, and presence of Anti-TSHR. The

Johns Hopkins Autoimmune Disease Research Center reports that there are 0.5 new cases per 1000 individuals per year.[25] Graves' Disease is associated with "decreased quality of life and significant morbidity from ophthalmological manifestations, osteoporosis and cardiovascular disease." [26]

The second type of AITD is Hashimoto Thyroiditis which occurs when inflammation caused by an autoimmune process destroys the thyroid gland, leading to an insufficient production of thyroid hormones (T3 and T4) leading to *hypothyroidism*. Diagnosis is normal FT4 but elevated TSH OR low FT4 and T3 but elevated TSH, and possible goiter. The Johns Hopkins Autoimmune Disease Research Center reports that there are 0.3–1.5 new cases of Hashimoto's Thyroiditis per 1,000 per year.[27] According to the U.S. National Library of Medicine, Hashimoto Thyroiditis can lead to development of a goiter, weight gain, and sometimes, thyroid cancer.[28]

Idiopathic Myxedema (IM), or complete hypothyroidism, has also been used as a marker for AITD in research.[29] It is characterized as atrophic thyroid gland, with positive auto-antibodies including TSH-stimulation blocking antibody (TSBAb).[30] Idiopathic Myxedema is the end stage of a lymphocytic thyroiditis in which humoral and cellular autoimmune processes lead to failure of the thyroid function. [31]

Graves' Disease, Hashimoto Thyroiditis, and Idiopathic Myxedema are all closely associated and tend to overlap throughout disease progression.[32] Patients can move from one diagnosis to another depending on the stage of their illness. For example, a patient may first be diagnosed with Hashimoto Thyroiditis but will later become hyperthyroid due to thyroid medications or natural progression of the disease.[32] Another example is a patient with Hashimoto Thyroiditis who ultimately develops IM. IM is a less specific autoimmune thyroid disease outcome, as it is not either Graves' or Hashimoto disease, but may capture participants who were diagnosed with hypothyroidism prior to or after developing Graves' Disease or Hashimoto Thyroiditis.

Previous Research

It is generally agreed upon that genetic predisposition accounts for nearly 70-80% of AITD development, but the onset of the disease must be triggered by exposure, such as an environmental factor.[33] Previous research has suggested that smoking, stress, infections, iodine consumption, certain medications as well as pollutants and radiation can be environmental triggers for AITD development.[33] Currently, there is not an established biological mechanism to explain how chronic airborne uranium exposure is associated with AITD, and therefore, it is

important to discuss previous research that has examined both the chemical toxicity and the radiologic potential of uranium and its relationship to AITD.

Early research in rats linked uranium poisoning to histological changes in the thyroid due to an autoimmune-like process.[8] Recent research with the DiNEH project (conference report), which examines mining-related health outcomes of Navajo people, found that participants exposed to more environmental uranium (based on their distance from waste sources) had increased production of activated T-cells and decreased activity of B cells.[34] The authors concluded that this can lead to lower production of protective antibodies and that the activated T-cells indicate that the immune system is highly reactive to some type of chemical hazard in the environment.[34] A study in Kyrgyzstan (conference report) which examined a city in an area where uranium ore had been heavily mined, found that all of the examined participants, who lived around the uranium biogeochemical zone, presented with altered TSH, T3, T4, Tg, and TPO antibodies in serum.[29] In a study utilizing a sample of 2007-2008 NHANES data, it was found that several heavy metals in the blood and urine are associated with altered thyroid hormones levels (Table 1).[9] Specifically, the study demonstrated that, in general, larger amounts of heavy metals in the blood and urine is associated with lower thyroid hormone levels, except for urinary Cadmium and Tungsten.[9]

Table 1. Associations of heavy metal body burdens on thyroid hormone levels (adapted from Yorita Christensen, 2013)[9]

Heavy Metal	Median Blood/Urine level	Thyroid Hormone Effect
Serum Cadmium	0.30 µg/L blood	↓TSH
Urinary Cadmium	0.20 µg/L urine	↑T3 ↑T4
Serum Mercury	0.90 µg/L blood	↓ T3 ↓T4
Urinary Thallium	0.15 µg/L urine	↓T4
Urinary Barium	1.50 µg/L urine	↓ T3 ↓T4
Urinary Cesium	4.60 µg/L urine	↓TSH
Urinary Tungsten	0.09 µg/L urine	↑TSH

In addition to the potential chemical toxicity of uranium and other heavy metals, exposure to ionizing radiation has been linked to AITD in studies examining nuclear plant accidents such as Chernobyl, and in atomic bomb survivors of Hiroshima and Nagasaki.[35,36] For example, the I^{131}radioactive fallout from the Hanford, Washington, Plutonium Production Site has been associated with increased thyroid cancer incidence among

residents downwind of the site.[18] More relevant to the circumstances of the population around Fernald is the association between occupational exposure to ionizing radiation and AITD observed by Volzke (2005) who found a strong exposure length dose-response among women.[37]

Although the exact mechanism of pathogenesis is not known, research to evaluate the association between uranium exposure and AITD in the FMMP population would help to establish the consistency of the observation. The surveillance data from the FMMP cohort is exceptionally strong and allows for temporal examination of chronic uranium exposure and AITD development. The cohort was carefully assembled from historical records and extensive community outreach, and represents a 25% sample of the exposed population in the vicinity of this plant. Importantly, the medical data of the FMMP is of high quality and is supplemented by health and behavior, and lifestyle data collected by annual questionnaires, allowing control for other potential determinates of AITD that has not been possible in previous research.

The considerable concern about AITD in the FMMP community, paired with the finding of elevated thyroid disease prevalence in the FMMP and new research suggesting a link between heavy metal exposure and thyroid hormone fluctuation, compelled us to use the FMMP data to determine if AITD is associated with exposure to uranium in the air among adult residents living near the former uranium processing facility.[20,9] Testing this hypothesis will provide answers that will inform a clinical area needing special diagnostic attention or provide reassurance to community concerns about this class of autoimmune disease.

Chapter 2 – Methods

A nested case-control study was conducted using the FMMP data in order to examine the association between autoimmune thyroid disease and cumulative airborne uranium exposure.

Subject Recruitment

In 1990, initial recruitment used local media to enroll 5,000 potential participants. In 1991, additional recruitment efforts mailed enrollment information to all the people who had applied for the FMMP settlement benefits.[11] Following approval from the Fernald Settlement Fund Trustees, applicants were offered a baseline examination. According to the CDC Dosimetry Reconstruction Project, about a quarter of the eligible Fernald area population is represented by the FMMP sample.[1] All participation was voluntary and at each exam informed consent was obtained from the participants.[11]

Study Population

The FMMP population includes individuals who had lived or worked in the five-mile radius of the FMPC, who resided there for at least two continuous years between January 1, 1952 and December 18, 1984, and who had not worked at the plant. (A separate monitoring program was designated for employees of the contractors National Lead of Ohio or National Lead Industries.[11]) Nearly 10,000 individuals meeting these criteria volunteered to participate in the FMMP. As shown in Figure 3, 8,787 met the inclusion criteria for this study: 1) at least 18 years of age at FMMP enrollment, 2) absence of an AITD before the baseline examination (n=227 removed), 3) absence of thyroid cancer diagnosis before baseline and during follow-up (n=18 removed), and 4) not taking thyroid medications at the baseline examination (n=63 removed).

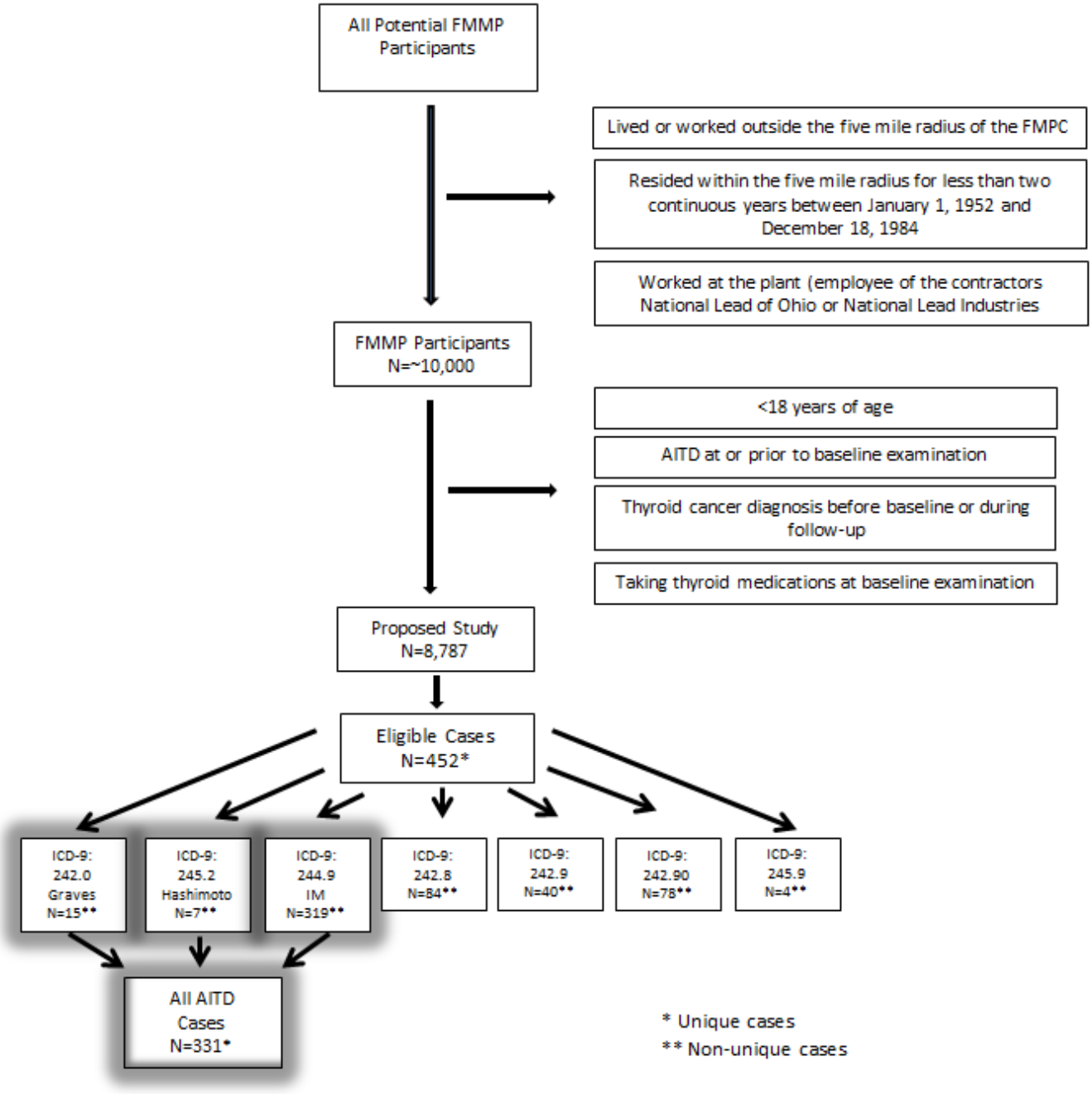
At the baseline examination, FMMP physicians collected a full medical history including illnesses, hospitalizations, procedures, and family medical history.[11] Over the 18 years of follow-up, FMMP physicians and nurses administered bi- or tri-annual physical examinations including laboratory tests of blood and urine, and several other medical diagnostic tests. Also, participants were asked to complete questionnaires every year. From the baseline examination and the follow-up examinations and questionnaires, all illnesses/disorders were assigned International Classification of Diseases, 9th revision (ICD-9) codes by Accredited Record Technicians.[11]

Case Definition (Autoimmune Thyroid Diseases)

Incident cases were identified if they met the inclusion criteria for the study and have been assigned at least one of the following ICD-9 codes: Hashimoto Thyroiditis (ICD-9: 245.2), Graves' Disease (ICD-9: 242.0), Idiopathic Myxedema (ICD-9: 244.9), Thyrotoxicosis of other specified origin (ICD-9: 242.8), Thyrotoxicosis without mention of goiter or other cause (ICD-9: 242.9), Thyrotoxicosis without mention of goiter, other cause, thyrotoxic crisis, or storm (ICD-9: 242.90), and other and unspecified chronic thyroiditis (ICD-9: 245.9) after the baseline examination. Of the participants considered cases, 87 were assigned multiple ICD-9 codes (up to 3 ICD-9 codes per patient) (Figure 3).

This study chose to examine four categories of autoimmune thyroid disease as primary outcomes: (1) "All AITD Cases" includes all unique cases of Graves' Disease, Hashimoto Thyroiditis, and Idiopathic Myxedema, (2) "Graves" includes all participants assigned a Graves' Disease ICD-9 code, (3) "Hashimoto" includes all participants assigned a Hashimoto Thyroiditis ICD-9 code, and (4) "Idiopathic Myxedema" includes all participants assigned an Idiopathic Myxedema ICD-9 code (Figure 3).

Figure 3. Incident case identification process (case groups shadowed)



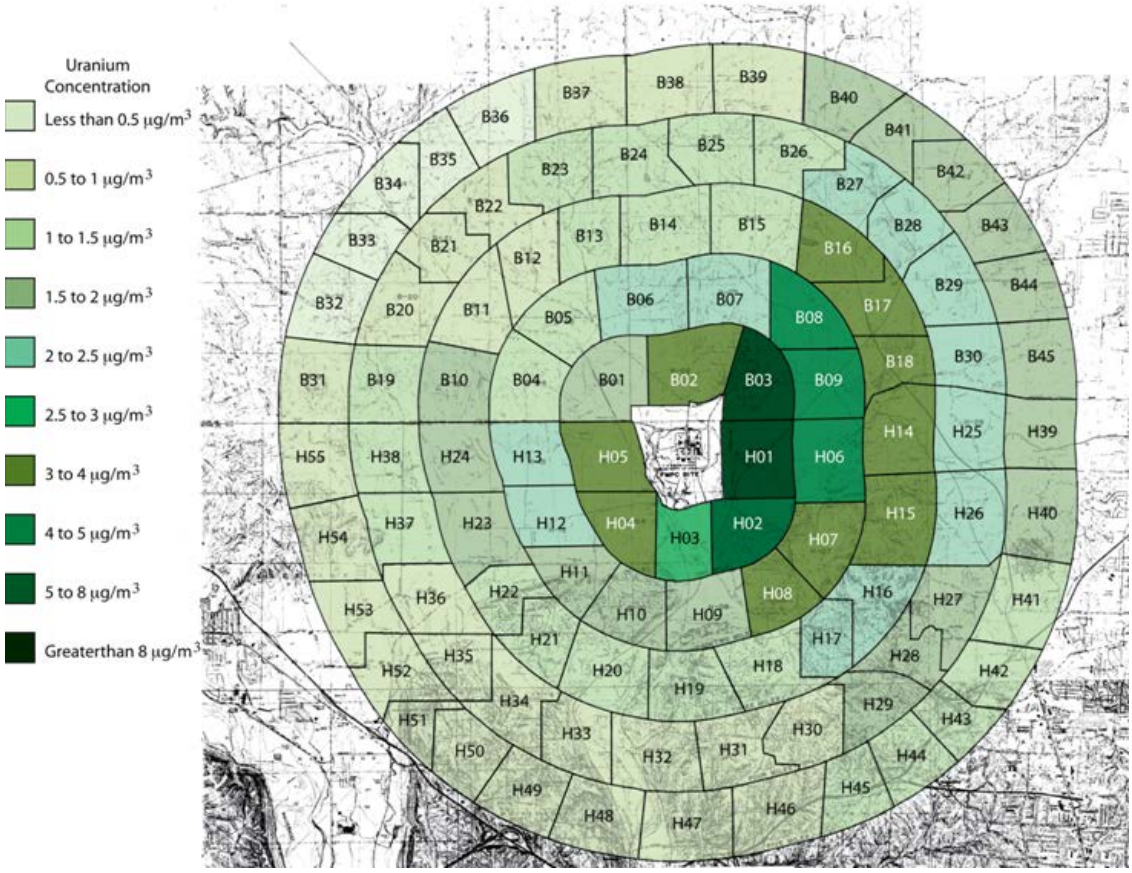
Control Selection

The same inclusion and exclusion criteria for cases were applied to controls. After cases were identified, all remaining participants in the cohort (n = 8,335) were considered as potential controls. Each *unique* case patient (n=452) was frequency matched by sex and year of birth to four controls in order to produce 1:4 matching. This frequency matching resulted in 1,808 controls.

Cumulative Airborne Uranium Exposure Group (Primary Explanatory Variable)

FMMP investigators established individual cumulative airborne uranium exposure estimates for each FMMP participant, and then categorized these estimates into three exposure groups. These exposure estimates represent the exposure pathway of inhalation. Individual exposure estimation was accomplished by applying the exposure algorithms, created by the CDC Fernald Dosimetry Reconstruction Project, to the FMMP exposure domain.[17] FMMP investigators divided the exposure domain, designated by the five-mile radius around the FMPC, into 100 segments and then calculated, for each segment, the average concentration of airborne uranium per year while accounting for "source term, particle size, dispersion and deposition, and distance and direction from the plant" (Figure 4).[17,38] Then, based on residence information collected from the annual FMMP questionnaires, FMMP investigators calculated each participants' yearly airborne uranium exposure based on where in the exposure domain they lived, when they lived there, and for how long. Finally, individual cumulative exposure estimates were calculated by summing exposure estimates for each participant for all years (ug/m^3).[17]

Figure 4. Cumulative Uranium Concentration (ug/m^3) of the Exposure Domain by Sector from 1951 to 1989 (ATSDR). Calculated for each exposure year, based on "source term, particle size, dispersion and deposition, and distance and direction from the plant".[38]



Three exposure groups were created based on the individual cumulative airborne uranium exposure estimates: *low* (estimated lifetime cumulative uranium exposure equivalent of <0.25 ug/m^3); *moderate* (0.25 to 0.50 ug/m^3); and *high* (>0.50 ug/m^3).[11,17] About 47% of FMMP adult participants were in exposure group 1 (low), 20% were in exposure group 2 (moderate), and 33% were in exposure group 3 (high).[11]

These exposure groups directly represent inhalation exposure to airborne particulates of uranium but also serve to indirectly represent exposure to beta radiation which is highly correlated with airborne uranium particle exposure.[11,20] FMMP investigators were able to estimate cumulative lifetime effective whole body radiation dose equivalents to each exposure group based on the CDC's nine hypothetical radiation dose scenarios and extensive research of "historical records of plant emissions, meteorological data, modeling of the dispersion and deposition of uranium-containing particulate matter, simulation studies, and comparison with results of exposure assessments performed at currently operating radiation-producing facilities."[17] The *low* airborne uranium exposure group with a lifetime radiation dose equivalent of 1.0 mSv beyond background uranium exposure represents the non-exposed population, because the exposure does not significantly exceed average annual background uranium exposures of 3.1 mSv.[2] The *moderate* airborne uranium exposure group has an estimated lifetime radiation dose equivalent of 5.5mSv beyond background exposure, and the *high* airborne uranium exposure group was estimated to have a lifetime radiation dose equivalent of 61mSv beyond background exposure.[17]

Covariates

Additional variables used for assessment of potential confounding included the following:

Age (age at FMMP enrollment): Graves' Disease and Hashimoto Thyroiditis are diagnosed most frequently between the ages of 20 and 40.[24] In the FMMP cohort, those in the *high* airborne exposure group tend to be older than those in the other two exposure groups. As age varies by exposure and outcome, it was controlled for by frequency matching each case to four controls by year of birth. Despite frequency matching, age was still considered a potential confounder as the frequency distributions may have changed when the different outcome categories were created.

Sex (male or female): Boelaert et al. (2010) reports a 5-10 fold higher prevalence of all AITDs among women than among men.[23] Sex may also differ by airborne uranium exposure group as those in the lowest exposure group were more likely to be male than those in the middle exposure group (Carin Waslo, Summer Practicum, p=.02). Women may also be affected by environmental exposures differently than men due to a generally smaller physical size, hormonal variation, and pregnancy.[15] In addition, during the 1950's and 1960's, women may be more likely to stay at home, and thus within the exposure area for greater periods of time than men who work outside of the home and exposure area. Despite frequency matching, sex was still considered a potential confounder as the frequency distributions may have changed when the different outcome categories were created.

Race (white or non-white): According to Schectman et al. (1991), TSH levels, and thus AITD's, vary by race.[39] Specifically, they found that race alone explained 5.5% of the variation in TSH levels between Whites and Blacks with Whites having significantly higher age and sex adjusted TSH levels.[39] The FMMP cohort is unique in that 99.5% of the participants are Non-Hispanic White.[11] Even so, it is possible that race varies by airborne uranium exposure group as those in the *high* exposure group were more likely to be White than those in the *low* exposure group (Carin Waslo, Summer Practicum, p=0.003).

Smoking (cumulative pack years): Holm et al. (2005) found that current cigarette smoking in women predicted development of Graves' Disease (HR: 1.93 (95%CI: 1.54-2.43) and found a positive dose response between the intensity of the smoking and the increased risk of Graves' Disease.[40] Interestingly, cigarette smoking has also been shown to be protective against hypothyroidism such as Hashimoto Thyroiditis due to smoking leading to lowered TSH levels.[41] Among the entire FMMP cohort, those in the *high* airborne uranium exposure group were more likely to be smokers than those in the *low* exposure group.[11] FMMP investigators created the variable "cumulative pack years" (CPY) which is equivalent to the number of packs/day multiplied by the number of years that the patient smoked that number of packs/day summed over follow-up time.

BMI: Holm et. al (2005) found that obesity (body mass index of 30 kg/m^2 or higher) in women was associated with a decreased risk of developing Graves' Disease.[40] BMI for study participants was calculated from each patient's earliest recorded weights and heights (nine participants earliest reported height and weight not at the baseline examination).

Family income, marital status, highest level of education: In the entire FMMP population, both income and education vary by airborne uranium exposure group as those in the *high* airborne uranium exposure group had lower incomes and were less likely to be high school graduates than those in the *low* exposure group.[11] Marital status could also vary by exposure status and therefore, all three of these variables were examined.

Data Management

There were 11 missing exposure estimates for 4 cases and 7 controls. Because none of the eleven had worked at the FMPC, the cumulative airborne uranium exposure estimate of 0.000345 ug/m^3 was imputed for the 11 missing exposures following standard FMMP investigator procedures, which corresponds to the minimum exposure value thus placing these participants in the *low* airborne uranium exposure group.

Three covariates had missing values: 20 missing values for marital status (18 controls, 2 cases), 24 missing values for education (23 controls, 1 case), and 132 missing values for annual household income (100 controls, 32 cases). Participants with missing values were not excluded from analysis, and each covariate was examined within each model for acceptability to be included in the model.

Original race categories included White, Hispanic, Asian/Pacific Islander, American Indian, and Other. Due to only one case and three controls being a race other than White, the race variable was categorized as "White" and "Non-white".

BMI was categorized into four groups, following the CDC's standard weight status categories (Table 4). Additionally, the categorization for marital status, highest level of education, and annual family income can be seen below.

Table 2. Categorical variable descriptions

BMI	Marital Status	Highest Level of Education	Annual Family Income
Underweight <18.5	Single	<=Some high school	<$20,000
Normal = 18.5 – 24.9	Separated	High school graduate	$20,000-34,999
Overweight = 25.0 – 29.9	Divorced	Some college	$35,999-49,000
Obese => 30	Married	College Graduate	50,000-74,999
	Widowed	Postgraduate	>$75,000
	Other	Vocational Training	

Statistical Analysis

All statistical analysis was conducted using STATA statistical software (version 12; Stata Corp, College Station, Texas). Statistical significance was set at $\alpha = 0.05$.

Descriptive Statistics

The relationship between AITD case categories and potential covariates was examined using independent two-sample t-tests for continuous covariates and Chi Square tests, or Fisher's exact test if expected cell counts were <5, for categorical covariates. The relationship between exposure groups and potential covariates was similarly examined. The overall relationship between case status and exposure group was examined using 3x2 Chi Square tests, or Fisher's exact test if expected cell counts were <5. The two-sample test of proportions was then used to compare proportions in exposure groups 1 versus 2, 2 versus 3, and 1 versus 3.

Univariate Analysis

We performed simple logistic regression to examine relationships between each outcome variable (All AITD cases, Graves, Hashimoto, IM) and all other study covariates. Covariates that significantly improved the model at the $\alpha = 0.25$ level were included in the variable selection procedure.

Variable Selection

A forward and backward stepwise variable selection was conducted, using all covariates indicated in the univariate analysis, in order to develop final models for the primary explanatory variable /AITD categories. Stepwise selection used the pr(0.25) pe(0.2) parameter. To find the preliminary main effect model, variables with a Wald test p-value of >0.05 significance were removed from the model.

Multivariate Analysis

Multivariate logistic regression was used to examine all exposure-outcome relationships, controlling for covariates indicated from the variable selection procedure.

To construct the main effects model, the distributions of the continuous covariates were assessed for normality and appropriate transformations were made. In order to ensure that the models with the transformed continuous variable was still the best model, all covariates previously removed were added back into the model one at a time and the models with and without the additional covariate were compared with Likelihood Ratio Tests.

Collinearity was a concern for the developing models because some of the covariates, namely income, education, and marital status, are likely associated with one another. Similarly, age and exposure are likely associated with one another. If collinearity was present, it would lead to unreliable β coefficients. Therefore, the Variance Inflation Factor (VIF) Approach of detecting collinearity was utilized to identify collinearity within the models.

Model diagnostics

Model diagnostic procedures utilized the Hosmer-Lemeshow Goodness of Fit test instead of Pearson's Chi-Square test. Next, for models with the continuous explanatory variable, the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were used to compare the model with transformed and untransformed explanatory variable to assess the best fit. Finally, the logistic regressions were visually assessed for outliers.

Chapter 3 – Results

Population Characteristics

Case-control stratified population characteristics are presented in Tables 3-4. The study population (1808 controls and 331 AITD cases) consisted of a larger percentage of women (76.4%) than men (23.6%), and almost all participants were White (99.8%). The mean age at FMMP entry was 48 years of age (Min: 18, Max: 87, SD: 14.16). Most participants were married (74.7%), had an annual household income of $0-$34,999 (52.0%), and achieved, at most, a high school graduate degree (39.1%). About 37.9% of participants had a BMI within the normal range, while 33.0% were overweight and 28.1% were obese. About 47% of participants smoked at some point during follow-up while 53% never smoked. Study participants who smoked had an average cumulative pack years (CPY) of 23.34 (Min: 0.05; Max: 162; SD: 20.97).

Relationship between AITD cases and potential covariates

AITD cases did not differ significantly from controls by sex, race, highest level of education, marital status, income, or BMI group (Table 3). While there is not a statistically significant difference between the mean age at FMMP entry between AITD cases and controls, controls do have a significantly higher smoking histories (mean CPY=11.48) than cases (mean CPY=10.85) (Table 4).

Table 3. Crude association between All AITD and potential categorical covariates [count(%)]

	Total	Controls	AITD Cases	p-value[a]
	n=2139	n=1808	n=331	
Sex				0.57
Female	1635	1378 (76.2)	257 (77.6)	
Male	504	430 (23.8)	74 (22.4)	
Race				0.60
White	2135	1805 (99.8)	330 (99.7)	
Non-White	4	3 (0.2)	1 (0.3)	
Marital				0.69[b]
Single	193	159 (8.8)	34 (10.3)	
Separated	18	17 (0.9)	1 (0.3)	
Divorced	192	166 (9.2)	26 (7.9)	
Married	1597	1345 (74.4)	252 (76.1)	
Widowed	118	102 (5.6)	16 (4.8)	
Other	1	1 (0.1)	0 (0.0)	
Educate				0.08
< = some high school	350	308 (17.0)	42 (12.7)	
High school graduate	837	718 (39.7)	119 (36.0)	
Some college	440	361 (20.0)	79 (23.9)	
College graduate	268	217 (12.0)	51 (15.4)	
Postgraduate	133	110 (6.1)	23 (7.0)	
Vocational training	87	71 (3.9)	16 (4.8)	
Income				0.40
< $20,000	556	483 (26.7)	73 (22.1)	
$20,000-$34,999	556	467 (25.8)	89 (26.9)	
$35,000-$49,999	456	387 (21.4)	69 (20.9)	
$50,000-$74,999	318	267 (14.8)	51 (15.4)	
$75,000-more	129	104 (5.8)	25 (7.6)	
BMI				0.09
Normal	810	703 (38.9)	107 (32.3)	
Underweight	24	18 (1.0)	6 (1.8)	
Overweight	705	586 (32.4)	119 (36.0)	
Obese	600	501 (27.7)	99 (29.9)	

[a] p-values based on $\chi 2$ analysis between exposure and outcome cell proportions.

[b] p-values based on Fisher's exact test.

* Indicates statistical significance for Chi-square test. Significance level set at α=0.05.

Table 4. Crude association between all AITD and potential continuous covariates [mean(SD)]

	Total	Controls	AITD Cases	t	p-value[a]
		n=1808	n=331		
Age[b]	47.72 (14.1)	47.81 (14.2)	47.72 (14.2)	0.71	0.48
CPY	10.85 (18.4)	11.48 (19.2)	10.85 (18.4)	3.68	<0.01*

[a] p-values based on two independent samples t-test

[b] Age at FMMP enrollment

* Indicates statistical significance. Significance level set at α=0.05.

Graves' Disease cases did not differ significantly from controls by sex, race, income, or BMI group. Regarding marital status, however, the proportion of singles among Graves' cases is significantly larger than the proportion of singles in controls. Also, Graves' cases were significantly more likely to have attended college, completed college, and attended post graduate schooling than controls (Table 5). There is not a statistically significant difference in mean CPY between cases and controls. Graves' cases (mean=36 years) were significantly younger than controls (mean=48 years) (Table 6).

Hashimoto cases did not differ from controls by sex, race, marital status, income, education, BMI group, age, or CPY (Table 5-6).

IM cases did not differ from controls by sex, race, highest level of education, marital status, or income. Regarding BMI group, however, more IM cases were overweight or obese compared to controls (Table 5). While there is not a statistically significant difference in mean age between IM cases and controls, IM cases had significantly less CPY (mean=7.64) than controls (mean=11.48) (Table 6).

Table 5. Crude association between AITD subgroups and potential categorical covariates [count(%)]

	Controls	Graves'	p-value[a]	Hashimoto	p-value[a]	IM	p-value[b]
	n=1808	n=15		n=7		n=319	
Sex			0.76		1.00		0.64
Female	1378 (76.2)	11 (73.3)		6 (85.7)		247 (77.4)	
Male	430 (23.8)	4 (26.7)		1 (14.3)		72 (22.6)	
Race			1.00		1.00		0.58
White	1805 (99.8)	15 (100.0)		7 (100.0)		318 (99.7)	
Non-White	3 (0.2)	0 (0.0)		0 (0.0)		1 (0.3)	
Marital			0.02*		0.30		0.84[a]
Single	159 (8.8)	6 (40.0)		1 (14.3)		30 (9.4)	
Separated	17 (0.9)	0 (0.0)		0 (0.0)		1 (0.3)	
Divorced	166 (9.2)	0 (0.0)		1 (14.3)		26 (8.2)	
Married	1345 (74.4)	9 (60.0)		4 (57.1)		244 (76.5)	
Widowed	102 (5.6)	0 (0.0)		1 (14.3)		16 (5.0)	
Other	1 (0.1)	0 (0.0)		0 (0.0)		0 (0.0)	
Educate			<0.01*		0.81		0.19
< = some high school	308 (17.0)	0 (0.0)		1 (14.3)		42 (13.2)	
High school graduate	718 (39.7)	2 (13.3)		3 (42.9)		117 (3.7)	
Some college	361 (20.0)	5 (33.3)		3 (42.9)		75 (23.5)	
College graduate	217 (12.0)	5 (33.3)		0 (0.0)		48 (15.1)	
Postgraduate	110 (6.1)	3 (20.0)		0 (0.0)		20 (6.3)	
Vocational training	71 (3.9)	0 (0.0)		0 (0.0)		16 (5.0)	
Income			0.09		0.94		0.44
< $20,000	483 (26.7)	3 (20.0)		2 (28.6)		69 (21.6)	
$20,000-$34,999	467 (25.8)	3 (20.0)		3 (42.9)		88 (27.6)	
$35,000-$49,999	387 (21.4)	3 (20.0)		1 (14.3)		66 (20.7)	
$50,000-$74,999	267 (14.8)	2 (13.3)		1 (14.3)		50 (15.7)	
$75,000-more	104 (5.8)	4 (26.7)		0 (0.0)		22 (6.9)	
BMI			0.44		0.90		0.03*
Normal	703 (38.9)	9 (60.0)		2 (28.6)		99 (31.0)	
Underweight	18 (1.0)	0 (0.0)		0 (0.0)		6 (1.9)	
Overweight	586 (32.4)	3 (20.0)		3 (42.9)		119 (37.3)	
Obese	501 (27.7)	3 (20.0)		2 (28.6)		95 (29.8)	

[a] p-values based on Fisher's exact test.

[b] p-values based on $\chi 2$ analysis between exposure and outcome cell proportions.

* Indicates statistical significance. Significance level set at α=0.05.

Table 6. Crude association between AITD subgroups and potential continuous covariates [mean(SD)]

	Controls n=1808	**Graves'** n=15	**t**	**p-value**[a]	**Hashimoto** n=7	**t**	**p-value**[a]	**IM** n=319	**t**	**p-value**[a]
Age[b]	47.8 (14.2)	35.9 (13.4)	3.3	<0.01*	44.4 (14.9)	0.52	0.60	47.6 (13.9)	0.3	0.80
CPY	11.5 (19.2)	6.9 (13.4)	0.9	0.36	7.7 (11.7)	0.63	0.53	7.6 (13.0)	3.4	<0.01*

[a] p-values based on two independent samples t-test

[b] Age at FMMP enrollment

* Indicates statistical significance. Significance level set at α=0.05.

Relationship between exposure groups and potential covariates

Exposure groups did not differ significantly by sex or race (Table 7). Regarding marital status, there was a larger proportion of single participants in the *low* airborne uranium exposure group compared to the *high* exposure group (Table 7). This seems reasonable considering that participants in the *low* exposure group also tended to be younger (mean=44 years) compared to the *high* exposure group (mean=53 years) (Table 8). There was a larger proportion of participants who had less than a high school degree and who had an annual household income of less than $20,000 in the *high* exposure group, compared to the lower exposure groups. Those in the *high* exposure group also had the largest proportion of obese individuals (Table 7). The CPY did not differ significantly by airborne uranium exposure group (Table 8).

Table 7. Crude association between cumulative airborne uranium exposure group and potential categorical covariates [count(%)]

	Total	Exp Group1 (Low)	Exp Group2 (Medium)	Exp Group3 (High)	χ^2	p-value
N(%)	2139	949 (44.4)	409 (19.1)	781 (36.5)		
Sex					2.5	0.28[a]
Female	1635	741 (78.1)	324 (79.2)	597 (76.4)		
Male	504	235 (24.8)	85 (20.8)	184 (23.6)		
Race						0.26[b]
White	2139	946 (99.7)	408 (99.8)	781 (100.0)		
Non-White	4	3 (0.3)	1 (0.2)	0 (0.0)		
Marital					53.7	<0.01*
Single	193	116 (12.2)	42 (10.3)	35 (4.5)		0.19[c]
Separated	18	7 (0.7)	3 (0.7)	8 (1.0)		0.95
Divorced	192	78 (8.2)	34 (8.3)	80 (10.2)		0.66
Married	1597	709 (74.7)	306 (74.8)	582 (74.5)		0.94
Widowed	118	32 (3.4)	20 (4.9)	66 (8.5)		0.35
Other	1	1 (100.0)	0 (0.0)	0 (0.0)		
Educate					59.6	<0.01[a]*
< = some high school	350	117 (12.3)	62 (15.2)	171 (21.9)		0.04[c]*
High school graduate	837	339 (35.7)	169 (41.3)	329 (42.1)		0.09[c]
Some college	440	224 (25.7)	83 (20.3)	133 (17.0)		0.06[c]
College graduate	268	142 (15.0)	50 (12.2)	76 (9.7)		0.28[c]
Postgraduate	133	74 (7.8)	21 (5.1)	38 (4.9)		0.60[c]
Vocational training	87	46 (4.9)	19 (4.7)	22 (2.8)		0.70[c]
Income					32.0	<0.01[a]*
< $20,000	556	208 (21.9)	100 (24.5)	248 (31.8)		0.02[c]*
$20,000-$34,999	556	242 (25.5)	110 (26.9)	204 (26.1)		0.88[c]
$35,000-$49,999	456	213 (22.4)	81 (19.8)	162 (20.7)		0.69[c]
$50,000-$74,999	318	161 (17.0)	59 (14.4)	98 (12.6)		0.34[c]
$75,000-more	129	73 (7.7)	24 (5.9)	32 (4.1)		0.50[c]
BMI					13.0	0.04*
Normal	810	379 (39.9)	162 (39.6)	269 (34.4)		0.15[c]
Underweight	24	14 (1.5)	1 (0.2)	9 (1.2)		0.95[c]
Overweight	705	315 (33.2)	131 (32.0)	259 (33.2)		0.99[c]
Obese	600	241 (25.4)	115 (28.1)	244 (32.2)		0.10[c]

[a] p-values based on $\chi 2$ analysis between exposure and outcome cell proportions.

[b] p-values based on Fisher's exact test.

[c] p-values based on two sample test of proportions, comparing exposure group 1 vs 3

* Indicates statistical significance for Chi-square test. Significance level set at α=0.05.

Table 8. Crude association between cumulative airborne uranium exposure group and potential continuous covariates [mean(SD)]

	Total	Exp Group1 (Low)	Exp Group2 (Medium)	Exp Group3 (High)	t[b]	p-value[a]	t[c]	p-value[a]	t[d]	p-value[a]
N(%)	2139	949 (44.4)	409 (19.2)	781 (36.5)						
Age[e]	47.7 (14.2)	44.0 (13.6)	46.7 (14.5)	52.8 (13.2)	-3.1	<0.01*	-13.5	<0.01*	-7.1	<0.01*
CPY	10.9 (18.4)	10.4 (17.6)	10.8 (18.7)	11.4 (19.3)	-0.3	0.74	-1.1	0.27	-0.6	0.58

[a] p-values based on two independent samples t-test , unequal variance

[b] Two independent samples t-test comparing exposure group 1 versus exposure group 2

[c] Two independent samples t-test comparing exposure group 1 versus exposure group 3

[d] Two independent samples t-test comparing exposure group 2 versus exposure group 3

[e] Age at FMMP enrollment

* Indicates statistical significance. Significance level set at α=0.05.

Relationship between case status and exposure group

Chi Square Tests indicate that there was no statistically significant relationship between airborne uranium exposure group and All AITD case status ($\chi^2(2)= 2.20$, p=0.33) or IM case status ($\chi^2(2) =1.34$, p=0.51). Fisher's Exact Test suggests that there was no statistically significant relationship between the exposure group and Graves' (p=0.38) or Hashimoto case status (p=0.42) (Table 9-10).

Table 9. Crude association between cumulative airborne uranium exposure group and all AITD [count(%)]

	Controls	AITD Cases	χ2	p-value
N(%)	1808 (84.5)	331 (15.5))		
Exposure Group			2.2	0.33[a]
Low	795 (44.0)	154 (46.5)		0.56[b]
Medium	341 (18.9)	68 (20.5)		0.75[b]
High	672 (37.2)	109 (32.9)		0.39[b]

[a] p-values based on 3x2 χ2 analysis between exposure and outcome cell proportions.

[b] p-values based on two sample test of proportions

* Indicates statistical significance. Significance level set at α=0.05.

Table 10. Crude association between cumulative airborne uranium exposure group and AITD subgroups [count(%)]

	Controls	Graves'	p-value	Hashimoto	p-value	IM	p-value
N(%)	1808 (99.2)	15 (0.8)		7 (0.4)		319 (17.6)	
Exposure Group			0.4[a]		0.4[a]		0.51[c]
Low	795 (44.0)	9 (60.0)	0.34[b]	4 (57.1)	0.60[b]	146 (45.8)	0.69[b]
Medium	341 (18.9)	3 (20.0)	0.96[b]	2 (28.6)	0.73[b]	65 (20.4)	0.78[b]
High	672 (37.2)	3 (20.0)	0.54[b]	1 (14.3)	0.64[b]	108 (33.9)	0.51[b]

[a] p-values based on Fisher's exact test.

[b] p-values based on two sample test of proportions

[c] p-values based on 3x2 χ2 analysis between exposure and outcome cell proportions.

* Indicates statistical significance. Significance level set at α=0.05.

Univariate statistics

Due to small samples sizes, the analysis for Graves and Hashimoto cases did not continue beyond Fisher's Exact Test for categorical exposure group. Univariate analysis for all AITD cases and Idiopathic Myxedema cases was conducted using simple logistic regressions for both categorical and continuous variables (Table 11).

All AITD Cases (n=331)

For those in the *medium* airborne uranium exposure group, the estimated odds of AITD is 1.03 times less likely than those in the *low* exposure group (95%CI: 0.75, 1.41, p=0.86) while the those in the *high* exposure group are 0.84 times less likely to have AITD than the *low* exposure group (95%CI: 0.64, 1.09, p=0.19). For AITD Cases, education, income, CPY and BMI group significantly improved the model at the alpha = 0.25 level and therefore were included in the variable selection procedure (Table 11).

The means for the continuous variable CPY was separately compared by case status using t-tests. The means for CPY were significantly different by case status with a difference of 4.05 pack years (t=3.68, p<.001) (Table 11).

Table 11. Estimated effect of covariate on AITD case status

Variable	β	95%CI, β	Std Error	OR	95% CI, OR	p-value
Exposure Group						
Low	Reference	Reference	Reference	Reference	Reference	0.33
Medium	0.03	-0.28, 0.34	0.16	1.03	0.75, 1.41	0.86
High	-0.18	-0.44, 0.09	0.14	0.84	0.64, 1.09	0.19
Age	0.00	-0.01, 0.01	0.00	1.00	0.99, 1.01	0.48
Sex	-0.08	-0.36, 0.20	0.14	0.92	0.70, 1.22	0.57
Race	-0.60	-2.87, 1.67	1.16	0.55	0.06, 5.29	0.60
Marital	-0.03	-0.15, 0.09	0.06	0.97	0.86, 1.10	0.64
Educate						
<=some high school	Reference	Reference	Reference	Reference	Reference	0.01*
high school graduate	0.20	-0.18, 0.57	0.19	1.22	0.83, 1.77	0.31
some college	0.47	0.07, 0.88	0.21	1.60	1.07, 2.40	0.02
College Graduate	0.54	0.10, 0.99	0.23	1.72	1.11, 2.69	0.02
Postgraduate	0.43	-0.13, 0.98	0.28	1.53	0.88, 2.67	0.13
Vocational Training	0.50	-0.13, 1.13	0.32	1.65	0.88, 3.11	0.12
Income						
<$20,000	Reference	Reference	Reference	Reference	Reference	0.10
$20,000-34,999	0.23	-0.10, 0.57	0.17	1.26	0.90, 1.76	0.17
$35,999-49,000	0.17	-0.19, 0.52	0.18	1.18	0.83, 1.68	0.36
50,000-74,999	0.23	-0.15, 0.62	0.20	1.26	0.86, 1.86	0.24
>$75,000	0.46	-0.04, 0.97	0.26	1.59	0.96, 2.63	0.07
Cumulative Pack Years	-0.01	-0.02, -0.01	0.00	0.99	0.98, 0.99	<.0001*
BMI group						
Normal	Reference	Reference	Reference	Reference	Reference	0.05*
Underweight	0.78	-0.16, 1.73	0.48	2.19	0.85, 5.64	0.10
Overweight	0.29	0.01, 0.57	0.14	1.33	1.01, 1.77	0.05*
Obese	0.26	-0.04, 0.56	0.15	1.30	0.97, 1.75	0.08

* Indicates statistical significance. Significance level set at α=0.05.

Idiopathic Myxedema (n=319)

For those in the medium airborne uranium exposure group, the estimated odds of IM is 1.03 times less likely than those in the *low* exposure group (95%CI: 0.75, 1.43, p=0.82) while the those in the *high* exposure group are 0.88 times less likely to have IM than the *low* exposure group (95%CI: 0.67, 1.15, p=0.33). For IM Cases, education, income, CPY and BMI group significantly improved the model at the alpha = 0.25 level and therefore were included in the variable selection procedure (Table 12).

The means for the continuous variable CPY was separately compared by case status using t-tests. Controls had a significantly higher CPY mean (M=11.48, SD=19.22) than cases (M=7.64, SD=13.01) with a difference of 3.84 pack years (t=3.43, p<.001).

Table 12. Estimated effect of covariate on IM case status

Variable	β	95%CI, β	Std Error	OR	95% CI, OR	p-value
Exposure Group						
Low	Reference	Reference	Reference	Reference	Reference	
Medium	0.04	-0.28, 0.36	0.16	1.04	0.75, 1.43	0.82
High	-0.13	-0.40, 0.14	0.14	0.88	0.67, 1.15	0.33
Age	0.00	-0.01, 0.01	0.00	1.00	0.99, 1.01	0.80
Sex	-0.07	-0.35, 0.22	0.14	0.93	0.70, 1.24	0.64
Race	-0.64	-2.90, 1.63	1.16	0.53	0.05, 5.10	0.58
Marital	0.00	-0.13, 0.12	0.06	1.00	0 .88, 1.13	0.98
Educate						0.02*
<=some high school	Reference	Reference	Reference	Reference	Reference	
high school graduate	0.18	-0.20, 0.56	0.19	1.19	0.82, 1.74	0.35
some college	0.42	0.01, 0.83	0.21	1.52	1.01, 2.29	0.04*
College Graduate	0.48	0.03, 0.93	0.23	1.62	1.04, 2.54	0.04*
Postgraduate	0.29	-0.29, 0.86	0.29	1.33	0.75, 2.37	0.33
Vocational Training	0.50	-0.13, 1.13	0.32	1.65	0.88, 3.11	0.12
Income*						
<$20,000	Reference	Reference	Reference	Reference	Reference	
$20,000-34,999	0.28	-0.06, 0.62	0.17	1.32	0.94, 1.85	0.11
$35,999-49,000	0.18	-0.19, 0.54	0.19	1.19	0.83, 1.72	0.34
50,000-74,999	0.27	-0.12, 0.66	0.20	1.31	0.88, 1.94	0.18
>$75,000	0.39	-0.13, 0.92	0.27	1.48	0.88, 2.50	0.14
Cumulative Pack Years*	-0.01	-0.02, -0.01	0.00	0.99	0.98, 0.99	0.00*
BMI group*						
Normal	Reference	Reference	Reference	Reference	Reference	
Underweight	0.86	-0.09, 1.81	0.48	2.37	0.92, 6.11	0.08
Overweight	0.37	0.08, 0.65	0.15	1.44	1.08, 1.92	0.01*
Obese	0.30	-0.01, 0.60	0.16	1.35	0.99, 1.82	0.06

* Indicates statistical significance. Significance level set at α=0.05.

The univariate analysis results indicated that, for both all AITD and IM cases, education, income, CPY, and BMI group were all significant at the 0.25 level. These variables were included in the following variable selection. Even though uranium exposures groups were far above p< 0.25 limit, they are included in the following stepwise procedures as they are the main exposure variable.

Variable Selection

Forward and backward stepwise (pr(0.25) pe(0.2)) model selection procedures were performed to produce multiple regression prediction models.

All AITD Cases

Both the forward stepwise and backward stepwise procedures indicated that education, CPY, and BMI group helped predict AITD case status. Therefore, the original model included education, CPY, and BMI group.

To construct the preliminary main effect model, variables with a Wald test p-value of >0.05 significance were removed from the model. Only CPY had p-values below 0.05.

In order to ensure that the variables removed were still insignificant when added back into the current preliminary main effects models, age, sex, race, marital, BMI group, income, and education were individually added back into the model. Likelihood ratio tests were performed comparing the current preliminary main effects model (CPY) with the model including the previously removed variable (age, sex, race, marital, educate, and income separately.) Results from the likelihood ratio test revealed that adding age back in the model was insignificant at the 0.05 level ($\chi^2(1)=0.05$, p=0.83), as was sex ($\chi^2(1)=.00$, p=0.97), race ($\chi^2(1)=0.32$, p=0.57), and BMI group ($\chi^2(3)=6.61$, p=0.09). Marital and income could not be compared via likelihood ratio test due to too many missing values.

Next, the beta coefficients from the univariate analysis were compared to the beta coefficients of the variables in the current preliminary main effects model. The coefficients did not change dramatically when CPY was included in the model (Univariate Analysis β= Original Model β). Therefore we concluded that the effect of each variable on AITD case status was not drastically attenuated when the other variables are included in the models.

Idiopathic Myxedema

Forward stepwise indicated that education, CPY, and BMI group helped predict IM case status while backward stepwise indicated that income additionally helped predict IM case status.

To identify the preliminary main effect model, variables with a Wald test p-value of >0.05 significance were removed from the model. Only BMI group and CPY have p-values below 0.05.

In order to ensure that the variables removed were still insignificant when added back into the current preliminary main effects model, age, sex, race, marital, education, and income, were individually added back into the model. Likelihood ratio tests were performed comparing the current preliminary main effects model (CPY and BMI Group) with the model including the previously removed variable (age, sex, race, marital, education, and income separately.) Results from the likelihood ratio test revealed that adding back in age was insignificant at the 0.05 level ($\chi^2(1)=0.00$, p=.0.98), as was sex ($\chi^2(1)=.15$, p=0.69), and race ($\chi^2(1)=0.33$, p=0.57). Again, marital, education, and income could not be compared via likelihood ratio test due to too many missing values. This confirms that the original analysis' conclusion that age, sex, race, marital, educate, and income should not be included in the model was correct.

Next, the beta coefficients from the univariate analysis were compared to the beta coefficients of the variables in the current preliminary main effects model. None of the coefficients changed dramatically when the other variables are included in the model (Table 13). Therefore we can conclude that the effect of each variable on Idiopathic Myxedema is not drastically attenuated when the other variables are included in the models.

Table 13. Comparing B coefficients between univariate analysis and current preliminary main effects model

Variable	N	Univariate Analysis β	Original Model β
BMI			
Normal	802	Reference	Reference
Underweight	24	0.86	0.84
Overweight	705	0.37	0.38
Obese	596	0.31	0.31
Cum Pack Years		-0.01	-0.01

Multivariate Analysis

All AITD Cases

To build the main effects model, the scale for CPY was examined to assess the linearity in the logit with a lowess curve. The lowess curves revealed that CPY did not have a very linear relationship with AITD but Gladder histograms by transformation plot didn't indicate that a transformation would be useful so CPY was kept untransformed.

A concern for this model was collinearity of the covariates. If collinearity was present, it would lead to unreliable β coefficients. However, the Variance Inflation Factor (VIF) Approach of detecting collinearity did not identify any collinear variables (VIF<10).

Idiopathic Myxedema

To construct the main effects model, the scale for CPY was examined to assess the linearity in the logit with a lowess curve. The lowess curves revealed that CPY did not have a very linear relationship with AITD but Gladder histograms by transformation plot didn't indicate that a transformation would be useful so CPY was kept untransformed.

The Variance Inflation Factor (VIF) Approach did not identify any collinear variables (VIF<10) in this model.

Model diagnostics

All AITD Cases

It is not appropriate to use Pearson Chi-Square test and/or Deviance based LRT because there is a continuous variable in the model, and therefore, Hosmer-Lemeshow goodness of fit test was used to assess goodness of fit instead. The HL test revealed that the model fits well because of the large p-value ($\chi^2(5)= 5.72$, p=. 0.33).

Next, the logistic regression was visually assessed for diagnostics using three plots: $\Delta Xj2\ vs.\pi\ j$, $\Delta Dj\ vs.\pi\ j$, and $\Delta\beta j\ vs.\pi\ j$. Two points in the top left corner identified potential covariate patterns that are poorly fit and were particularly suspect. Next the plot of $\Delta Xj2\ vs.\ \pi j$ with symbol size proportional to $\Delta\beta j$ was examined to assess the size of the observations in the top left corner. The large points were suspicious. Upon further examination of the top four influential observations, observations 1870 and 3068 had the highest Cook's D, chgPearsons, and chgDev values which indicated that they were potentially influential outliers and should be further evaluated.

The original model was compared to the model without 1870 and to the model without 3068 and the percent change in the coefficients from the original model was less than 10% for all coefficients. Therefore, the two observations were not removed.

Idiopathic Myxedema

It is not appropriate to use Pearson Chi-Square test and/or Deviance based LRT because there is a continuous variable in the model, and therefore, Hosmer-Lemeshow goodness of fit test was used to assess goodness of fit instead. The HL test revealed that the model fits well because of the large p-value ($\chi^2(8)= 4.82$, p=. 0.78).

Next, the logistic regression was visually assessed for diagnostics using three plots: $\Delta Xj2\ vs.\pi\ j$, $\Delta Dj\ vs.\pi\ j$, and $\Delta\beta j\ vs.\pi\ j$. The point in the top left corner identified potential covariate patterns that are poorly fit and was particularly suspicious. Next the plot of $\Delta Xj2\ vs.\ \pi j$ with symbol size proportional to $\Delta\beta j$ was examined to assess the size of the observations in the top left corner. The large observation in the left top corner was suspicious. Upon further examination of the top four influential observations, observations 6172 and 4168 had the highest Cook's D, chgPearsons, and chgDev values which indicated that they were potential outliers and should be closely evaluated.

The original model was compared to the model without 6172 and to the model without 4168 and the percent change in the coefficients from the original model was less than 10% for all coefficients. Therefore, the two observations were not removed.

Final model and interpretation

All AITD Cases

The final model includes exposure group and CPY with 4 parameters (Table 13).

$g(x) = logit\big(\pi(x)\big)$ =βhat0 + βhat1*exposure group2 + βhat2* exposure group3+ βhat3* CPY

$g(x) = logit\big(\pi(x)\big)$ =-1.51+ 0.03 *exposure group2 + -0.17 *exposure group3+ -0.01* CPY

The estimated OR of AITD among participants in the medium exposure group is 1.03 times more likely than participants in the lowest exposure group (95%CI: 0.75, 1.41) when controlling for CPY. The estimated OR of AITD among participants in the highest exposure group is 0.85 times less likely than participants in the lowest exposure group (95%CI: 0.65, 1.10) when controlling for CPY.

The estimated Odds Ratio (OR) for CPY is 0.9853, suggesting that a 1 year increase in CPY is associated with a 1.47% decrease in the predicted odds of Idiopathic Myxedema in the patient population, when controlling for exposure group and BMI group (95%CI: 0.98, 0.99).

Table 14. Final model for AITD, exposure group, and covariate

Variable	β	95%CI, β	Std Error	OR	95% CI, OR	p-value
Exposure Group						
1	Reference	Reference	Reference	Reference	Reference	
2	0.03	-0.28, 0.35	0.16	1.03	0.75, 1.41	0.84
3	-0.17	-0.43, 0.10	0.14	0.85	0.65, 1.10	0.22
Cumulative Pack Years	-0.01	-0.02, -0.01	0.00	0.99	0.98, 0.99	<.01

Idiopathic Myxedema

The final model includes exposure group, CPY, and BMI group with 7 parameters (Table 14).

$g(x) = logit(\pi(x))$ = βhat0 + βhat1*exposure group2 + βhat2* exposure group3+ βhat3* CPY + βhat4*bmigrp2 + βhat5*bmigrp3 + βhat6*bmigrp4

$$g(x) = logit(\pi(x)) = -1.80 + 0.05 * \text{exposure group2} + -0.14 * \text{exposure group3} + -0.01 * \text{CPY} + 0.86 * \text{bmigrp2} + 0.38 * \text{bmigrp3} + 0.31 * \text{bmigrp4}$$

The estimated odds of Idiopathic Myxedema among underweight FMMP participants is 2.35 times more likely than participants with a normal BMI (95%CI: 0.91, 6.10) when the exposure group and CPY are controlled. The estimated odds of Idiopathic Myxedema among overweight FMMP participants is 1.46 times more likely than participants with a normal BMI (95%CI: 1.09, 1.95) when the exposure group and CPY are controlled. The estimated odds of Idiopathic Myxedema among obese FMMP participants is 1.37 times more likely than participants with a normal BMI (95%CI:1.01, 1.86) when the exposure group and CPY are controlled.

The estimated OR for CPY is 0.996, suggesting that a 1-year increase in CPY is associated with a 1.38% decrease in the predicted odds of Idiopathic Myxedema in the FMMP population, when controlling for exposure group and BMI group (95%CI: 0.98, 0.99).

The estimated OR of Idiopathic Myxedema among participants in the medium airborne uranium exposure group is 1.05 times more likely than participants in the lowest exposure group (95%CI: 0.76, 1.45) when controlling for CPY and BMI group. The estimated OR of Idiopathic Myxedema among participants in the highest exposure group is 0.87 times less likely than participants in the lowest exposure group (95%CI: 0.66, 1.14) when controlling for CPY and BMI group.

Table 15. Final model for Idiopathic Myxedema, exposure group, and covariates

Variable	β	95%CI, β	Std Error	OR	95% CI, OR	p-value
Exposure Group						
1	Reference	Reference	Reference	Reference	Reference	
2	0.05	-0.27, 0.37	0.16	1.05	0.76, 1.45	0.77
3	-0.14	-0.41, 0.13	0.14	0.87	0.66, 1.14	0.31
BMI group						
Normal	Reference	Reference	Reference	Reference	Reference	
Underweight	0.86	-0.10, 1.81	0.49	2.35	0.91, 6.10	0.08
Overweight	0.38	0.09, 0.67	0.15	1.46	1.09, 1.95	0.01
Obese	0.31	0.01, 0.62	0.16	1.37	1.01, 1.86	0.05
Cumulative Pack Years	-0.01	-0.02, -0.01	0.00	0.99	0.98, 0.99	<.01

In addition, a complete analysis was conducted using the *continuous* cumulative airborne uranium exposure estimates (ug/m^3) in place of the *low-medium-high* categorization. Similarly, this analysis did not demonstrate an association between airborne uranium exposure and AITD or IM. Results for the representation of exposure as a continuous variable are presented in Appendix A.

Chapter 4 – Discussion

This study utilized the FMMP cohort surveillance data in order to examine the relationship between chronic airborne uranium exposure and the incidence of autoimmune thyroid disease. We failed to demonstrate an association between cumulative uranium exposure and any of the four AITD categories: all AITD cases, Graves' Disease, Hashimoto Thyroiditis, and idiopathic myxedema. Likewise, when exposure was characterized as a continuous variable, no association was observed.

Public Health Implications

The FMMP's main objective was to "identify disease if present or to reassure those found to be healthy" in order to reduce emotional distress and to address the community health concerns.[11] Worry about thyroid diseases frequently arose when residents in the areas near Fernald have been questioned about health concerns.[15] In 2003, Pinney et al. reported an elevated prevalence of several health outcomes including thyroid disease among FMMP participants compared to national data.[20]

Autoimmune thyroid diseases are the most common autoimmune diseases in the US., and are associated with reduced quality of life and co-morbidity from ophthalmological manifestations, osteoporosis and cardiovascular disease.[42] These consequences are not insignificant, and are likely associated with large health care costs. Due to recent literature suggesting potential associations between heavy metal exposure and autoimmune thyroid disease, we decided that examining the association in the FMMP population may provide answers that would either highlight a clinical area needing special diagnostic attention or that would help to address community concerns about an autoimmune disease.

Our results did not demonstrate an association between cumulative airborne uranium exposure and any of the AITD categories in the FMMP population. While the community should be made known of the limitations of our analysis, we would suggest that AITD should not be a priority concern for the exposed residential population around Fernald. We believe that standard thyroid disease screening and treatment procedures provide sufficient protection for this population.

Potential Limitations and Strengths of the Study Design

As one of the largest environmental hazard related medical monitoring programs funded by a class action lawsuit, the FMMP provides a data set of almost 10,000 participants that has been coded and computerized for easy analysis. The data set includes almost complete demographic, medical history, and residential information for each participant along with data from 18 years of laboratory tests of blood and urine, and several other medical diagnostic tests. In addition, about 160,000 biospecimens were collected and biobanked. From the yearly questionnaire data, risk factor matrices for cumulative cigarette pack-years, family history of cancer types, and family structure information were developed for examination of potential covariates.

The cohort is composed of both participants that were exposed to radiation and uranium above background levels and participants who were not, which allows for construction of three exposure comparison groups (CDC Fernald Dosimetry Reconstruction Project), making exposure-outcome analyses efficient. The FMMP is a major resource for the study of the adverse health effects of low-level radiation, uranium exposure, and related issues.

The availability of such a cohort allows this current study to utilize a "nested" case-control study design, cases and controls are selected from a prospective cohort, which reaps the benefits of both a cohort design and a traditional case-control design. Specifically, a "nested" case-control study ensures that exposure precedes the occurrence of disease, allows for examination of rare outcomes, allows matching to control several covariates, and minimizes selection bias associated with self-referral into the FMMP.

Due to the significant public health implications of these results, it is important to address the potential chance, bias, and confounding that may have prevented our ability to find an association when there truly is an association between airborne uranium exposure and AITD in the FMMP population. Additionally, Hill's considerations for evaluating evidence of causality will be examined in the following discussion.[43]

Chance

The statistical analysis found that the associations between continuous and categorical uranium exposure and all of the AITD categories were all insignificant at the α=0.05 level, and in fact, we all close to the null. This,

combined with the reasonably narrow 95% confidence intervals for all of the examined association combinations, suggests that there is little uncertainty about the results.

A potential limitation is the small sample sizes for Hashimoto Thyroiditis (n=7) and Graves' Disease (n=15) cases (Type-II error). *A priori* power calculations indicated that the minimum detectable effect sizes were quite large for these two AITD categories. It is possible that an association was not found due to lack of power to detect a small effect size. We suggest that the null associations found for Graves' Disease and Hashimoto Thyroiditis be considered with caution as we did not have the statistical power to assess the association appropriately.

Bias

We do not believe that either selection bias or information bias resulted in underestimating the magnitude of the examined associations.

Selection Bias: One potential limitation to this study is that participation in the FMMP cohort was voluntary and therefore the study group is not representative of the entire population within the Fernald exposure area. According to the CDC Dosimetry Reconstruction Project, about a quarter of the eligible Fernald area population is represented by the FMMP sample which allowed the possibility of a "healthy volunteer effect". If many FMMP participants who had developed AITD were too ill to participate in the FMMP, their disease would not be included in the analysis which would underestimate the magnitude of association. However, we do not believe this occurred as examination of demographic information of the FMMP sample revealed that education, income, smoking status, and standardized mortality ratios of cardiovascular disease during the first years of follow-up were similar to the general Fernald population.[11]

On the other hand, if FMMP residents who had more health problems and perceived themselves as having higher exposure volunteered at a greater rate than those who were perceived themselves as healthier and having lower exposure, there would be an overrepresentation of those with the worst health. However, this would only bias the results away from the null, and considering our null results, we are confident this did not occur.

Information Bias: Reconstruction of historical exposure and dose histories was conducted for all participants in the FMMP cohort without knowledge of health status and years before this case-control study was conducted. Therefore, identical methods were applied to estimate prior exposure to airborne uranium particles in

the case and control groups. While uncertainties exist in the variables used in the atmospheric dispersion models and dose estimates, our use of broad exposure categories accounted for inherent imprecision. Our analysis treating exposure as a continuous variable yielded similar null findings to our categorical approach. Survey information on BMI and smoking was collected at baseline before the appearance of thyroid disease, minimizing reporting bias by health status.

Temporality

Due to the utilization of a "nested" case-control study design, cases and controls were selected from a prospective cohort, we were able to ensure temporality by selection only incident cases that were diagnosed with AITD after the baseline FMMP examination. Therefore, we are confident that the exposure preceded the outcome and there is no concern for reverse causality.

Confounding

This analysis is secondary and therefore the data were not originally collected with the intention to test the association to autoimmune thyroid disease. Therefore, some potential confounders were not measured and could not be included in the analysis. For example, there is an established association between iodine consumption in the diet and thyroid disease. According to Laurberg et al. (1998), long-standing high iodine consumption can lead high TSH levels and hypothyroidism while long-standing low iodine consumption can lead to low TSH and hyperthyroidism.[44] This is likely not an issue, however, because there is no reason to believe that residents of Ohio would consume a great deal of fish or have a significantly insufficient amount of iodine in their diet.

There is an established hereditary component for autoimmune thyroid disease, but complete family history of this specific disease was not collected. Although we could not control for family history in the multivariable analysis, there is no immediately obvious reason for those without a family history of AITD to be more concentrated in the *high* vs. *low* exposure groups.

There is also a well-established, mutually influential relationship between diabetes and thyroid diseases. Specifically, "thyroid hormones contribute to the regulation of carbohydrate metabolism and pancreatic function, and on the other hand, diabetes affects thyroid function tests to variable extents".[45] While diabetes was not

examined in this analysis, it does not seem reasonable that those with diabetes would be more concentrated in the *low* exposure group.

While we were unable to control for the potential confounders discussed above, we were able to adjust the models for several other important covariates, smoking and Body Mass Index (BMI), which both have previously established relationships to thyroid function.[41,40] As would be expected from previous research, results from this study showed that smoking was associated with a decreased risk and being overweight or obese was associated with an increased risk of hypothyroidism (IM), if the odds ratios were assumed to approximate risk. The consistency of these associations with the relationships previously established in the literature helps to validate our statistical models, despite being unable to control for every potential covariate.

In summary, we do not believe that our lack of control for these potential cofounders could obscure associations between our exposures and outcomes.

Strength

The largest crude effect size for any of the exposure-outcome combinations was an odds ratio of 1.04 (95%CI: 0.75, 1.43) between Idiopathic Myxedema in the *medium* exposure group compared to the *low* exposure group. Among the adjusted effect sizes, an odds ratio of 1.05 (95%CI: 0.76, 1.45) was found between Idiopathic Myxedema in the *medium* exposure group compared to the *low* exposure group. The associations are weak in magnitude and do not provide strong support for a causal association.

Specificity

Data collection methods included FMMP physician-performed history and physical examinations, frequently used questionnaires in health assessment research, the American Thoracic Society questionnaire, and the SF-36 health perception instrument.[11] All data from examinations, questionnaires, and lab tests were entered into SAS by Accredited Record Technicians.

Exposure estimates were generated using the CDC Radiological Assessments Corporation dosimetry reconstruction algorithms. The very nature of environmental exposures makes it difficult to accurately capture the people who were exposed, exactly to what they were exposed, by which exposure pathway they encounter

exposure, and the amount and duration of that exposure. Therefore, despite expertise in exposure estimation, the airborne uranium exposure estimates used in this study are, by nature, imperfect. They are, however, the very best that are available. Furthermore, exposure was examined as both a categorical and a continuous variable. Categorizing the exposure into three exposure groups decreased the degree of misclassification that was inherently present in the continuous exposure variable.

ICD-9 codes were used to establish outcomes. As O'Malley et al. (2005) illustrates, common errors with ICD-9 coding includes "the clinician's knowledge and experience with the illness, and the clinician's attention to detail...coder training and experience, facility quality-control efforts, and unintentional and intentional coder errors, such as misspecification, unbundling, and upcoding."[46] Although AITD was diagnosed by physicians and lab reports, and all self-reported illnesses on questionnaires were verified with medical records, AITD was not an initial concern for FMMP participants. It is therefore possible that physicians paid less attention to accurately capturing and coding the different classifications of thyroid disease, and specifically AITDs. For example, thyroid disease can transition from hyperthyroidism to hypothyroidism, or vice versa, in its progression toward AITD. Perhaps participants were misclassified as the more general coding for Idiopathic Myxedema while they truly should have been classified as Hashimoto Thyroiditis. Since this study found a null association for Idiopathic Myxedema, however, this misclassification concern appears unlikely.

In an effort to address our concerns of outcome misclassification, we preformed analyses on additional categorizations of the FMMP data. For example, as many participants in our study were assigned multiple ICD-9 codes over the 18-year follow-up period, we categorized the outcomes to include only the initial diagnoses for four clinically relevant groups (Group 1: ICD-9 242.0; Group 2: 242.8, 242.9, and 242.90; Group 3: 244.9; and Group 4: 245.2, 245.9). We also categorized the outcomes into whether the participant was initially diagnosed with hyperthyroidism or hypothyroidism. No analysis suggested an association between either categorical or continuous measures of airborne uranium exposure and increased risk of any of the AITD groups (See Appendix B-H).

In addition, all diseases and conditions were assigned International Classification of Diseases, 9th revision (ICD-9) codes by Accredited Record Technicians. ICD codes and medical chart information was verified by double

data entry into a SAS database and SAS Compare. Any inconsistencies were corrected after the original paper chart was consulted.

Although every effort was made to establish accurate exposure estimates and ICD-9 codes, we acknowledge the limitations of these measurements. We are, however, reasonably confident from our additional analyses, that misclassification of outcome did not result in underestimation of association.

External Consistency and Biological Plausibility

It is important to evaluate our findings in light of previous reports on AITD and environmental exposures. As previously mentioned, our investigation was motivated by the report of Pinney et al. (2003) describing an elevated prevalence of thyroid disease at enrollment, not otherwise specified, in the FMMP population compared to national survey data from the NHIS.[20] The study by Christensen (2012) reported an association between altered thyroid hormones and levels of heavy metals in blood and urine, however the investigators did not examine uranium specifically[9]. Further, this was a cross-sectional study of NHANES data, so it was not possible to evaluate the temporal course of exposure and the occurrence of altered thyroid hormones.

Further, the study by Volzke et al. (2005) that demonstrated an association between occupational radiation exposure and thyroid hormone alterations had many limitations that may explain our differing findings. The Volzke study design was cross-sectional, used a dichotomous exposure (none vs some), and used self-reported information on exposure.[37]

Although these studies suggest an association between heavy metal exposure and uranium for AITD, we are not surprised by null finding given the methodologic limitations of the previous investigations.

A relationship between ionizing radiation and thyroid disease has been reported in multiple studies examining nuclear plant accidents such as Chernobyl, and in atomic bomb survivors of Hiroshima and Nagasaki.[35,36] However, the type and extent of exposure to ionizing radiation in these studies differs substantially from the exposure experience of the FMMP population. Both the CDC and the National Academy determined that 90% of the total radiation exposure from the FMPC was from alpha radiation, primarily via radon gas, with almost no opportunity for internal beta exposure. Furthermore, the ATSDR concluded that the amount of direct radiation exposure that residents may have received was not sufficient to cause adverse health effects.[15] In addition, the

FMPC, unlike the Hanford Plutonium Production Site, did not release Iodine^{131}, which is known to be associated with autoimmune thyroiditis with or without hypothyroidism and thyroid cancer.[1,18]

Dose-Response

No dose-response pattern was observed in our data. In fact, relative to the low airborne uranium exposure group, the *high* exposure group often had smaller ORs than those in the *medium* exposure group. The lack of a consistently increasing dose-response pattern from low to medium to high exposure groups is evidence against a causal relationship.

Future Research

Although we did not demonstrate an association between airborne uranium exposure and AITD, future investigations may want to examine the joint effect of uranium inhalation and ingestion from water sources. For this study, we were unable to do this due to missing values for water source exposure estimates and the differing methods used to create the exposure estimates.

The dosimetry reconstruction project examined this second exposure pathway involving the ingestion of uranium from consuming water from privately owned wells and cisterns.[1,15] An estimated 99,000 kg of uranium was released into surface water around the plant between 1952 and 1989.[11] 226Ra and 228Ra were the most important potential contributors to offsite radiation dose that were released into surface water. The main sources of groundwater contamination were concentrated in the South Plume, and attributed to uranium contaminated water being released to the storm sewer outfall ditch and Paddy's Run Creek. Both of these sources empty into the Great Miami Aquifer which supplied drinking water to privately owned wells in the Fernald area. About 48% of residents reported in a baseline questionnaire that they used a well as their drinking water source, and about 30% used a cistern.[15] The CDC Fernald Dosimetry Reconstruction Project, using data from monitored wells and groundwater modeling, estimated body doses of 0.04-0.3 mg/kg/day for a child and 0.02-0.1 mg/kg/day for an adult, both of which exceed the health-based guideline of 0.002 mg/kg/day for ingested uranium.[15] A full description of the estimated exposure pathways and doses can be found in the final release of the ASTDR Public Health Assessment for the FMPC.[15]

In addition, further research should be conducted to examine ionizing radiation exposure to the thyroid specifically. A grant application is currently being drafted to cover the costs of extending the CDC algorithm to calculate the radiation doses to the thyroid.

Finally, future investigations should utilize more sophisticated methods of analysis, such as survival models, in order to account for varying amounts of follow-up time among FMMP participants.

Conclusions

The surveillance data from the FMMP cohort is exceptionally strong and allows for examination of chronic uranium exposure and incidence of diseases such as AITD. The cohort was carefully assembled from historical records and extensive community outreach, and represents a 25% sample of the exposed population in the vicinity of this plant. Importantly, the medical data of the FMMP is of high quality and is supplemented by health, behavior, and lifestyle data collected by annual questionnaires, allowing control for other potential determinants of AITD that has not been possible in previous research.

We did not find an association between cumulative airborne uranium exposure and any of the AITD categories in the FMMP population. While the community should be made aware of the limitations of our study, our findings indicate that if risk of AITD is elevated in the population around Fernald, the excess incidence is very small and other diseases should receive priority in research, surveillance and treatment.

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Appendix

A. Statistical analysis and results for continuous exposure

Population Characteristics

Relationship between continuous exposure and potential covariates

The average cumulative uranium exposure did not differ significantly by sex or race. Participants who are single, had achieved at least a high school graduate degree, had earned more than 35,000 dollars a year, and are normal weight, on average, have significantly less ug/m3 cumulative exposure.

Crude association between cumulative continuous airborne uranium exposure and potential categorical covariates

	Total n=2139	**Mean (SD) ug/m^3**	**t**	**p-value[a]**
Sex			0.0	1.00
Female	1635	0.7 (0.9)		
Male	504	0.7 (1.1)		
Race			-1.1	0.27
White	2139	0.7 (1.0)		
Non-White	4	0.2 (0.1)		
Marital				
Single	193	0.4 (1.0)	Reference	Reference
Separated	18	0.7 (1.0)	-1.2	0.22
Divorced	192	0.8 (1.1)	-3.7	<0.01*
Married	1597	0.7 (0.9)	-4.3	<0.01*
Widowed	118	1.0 (1.0)	-5.1	<0.01*
Other	1	-	-	-
Educate				
< = some high school	350	1.0 (1.1)	Reference	Reference
High school graduate	837	0.7 (0.9)	4.9	<0.01*
Some college	440	0.6 (1.0)	5.3	<0.01*
College graduate	268	0.5 (0.8)	6.3	<0.01*
Postgraduate	133	0.6 (1.0)	3.7	<0.01*
Vocational training	87	0.5 (0.7)	4.0	<0.01*
Income				
< $20,000	556	0.8 (1.1)	Reference	Reference
$20,000-$34,999	556	0.7 (1.0)	1.6	0.11
$35,000-$49,999	456	0.6 (0.9)	3.1	<0.01*
$50,000-$74,999	318	0.5 (0.7)	4.4	<0.01*
$75,000-more	129	0.4 (0.7)	3.9	<0.01*

BMI				
Normal	810	0.6 (0.9)	Reference	Reference
Underweight	24	0.9 (1.9)	-1.5	0.12
Overweight	705	0.7 (1.0)	-2.0	0.04*
Obese	600	0.7 (1.0)	-2.0	0.05

[a] p-values based on two sample t-tests.

* Indicates statistical significance at level set at α=0.05.

Relationship between case status and continuous exposure

Two sample t-tests suggest that there is no statistically significant relationship between the exposure and any of the AITD categories.

Crude association between cumulative airborne uranium exposure and all AITD

	Controls	AITD Cases	t	p-value[a]
N(%)	1808 (84.5)	331 (15.5)		
Exposure Mean (SD)	0.69 (0.98)	0.63 (0.90)	1.0	0.30

[a] p-values based on two sample t-test

* Indicates statistical significance. Significance level set at α=0.05.

Crude association between cumulative airborne uranium exposure and AITD subcategories

	Controls	Graves	p-value[a]	Hashimoto	p-value[a]	IM	p-value[a]
N(%)	1808 (99.2)	15 (0.8)		7 (0.4)		319 (17.6)	
Exposure Mean (SD)	0.69 (0.98)	0.63 (1.2)	0.81	0.28 (0.43)	0.27	0.64 (0.90)	0.40

[a] p-values based on two sample t-test

Univariate statistics

All AITD Cases (n=331)

The β coefficient for continuous airborne uranium exposure is -0.07, suggesting that a 1 ug/m^3 increase airborne uranium exposure is associated with a -0.07 decrease in the log odds of AITD (95%CI: -0.20, 0.06, p=0.29).

Variable	B	95%CI, B	Std Error	OR	95% CI, OR	G	p-value
Continuous Exposure (ug/m^3)	-0.07	-0.20, 0.06	0.07	0.93	0.82, 1.06	1.19	0.29
Log Continuous Exposure (ug/m^3)	-0.05	-0.12, 0.02	0.04	0.95	0.89, 1.02	1.85	0.17

Idiopathic Myxedema (n=319)

The β coefficient for continuous airborne uranium exposure is -0.06, suggesting that a 1 ug/m^3 increase airborne uranium exposure is associated with a -0.06 decrease in the log odds of AITD (95%CI: -0.19, 0.07, p=0.39).

Variable	B	95%CI, B	Std Error	OR	95% CI, OR	G	p-value
Continuous Exposure (ug/m^3)	-0.06	-0.19, 0.07	0.07	0.94	0.83, 1.07	0.78	0.39
Log Continuous Exposure (ug/m^3)	-0.04	-0.11, 0.04	0.04	0.96	0.90, 1.04	0.91	0.34

Variable Selection

All AITD Cases

Both the forward stepwise and backward stepwise procedures indicated that education, CPY, and BMI group helped predict AITD case status. After the Wald test, where variables with a p-value of >0.05 significance were removed from the model, only education and CPY remained in the model.

In order to ensure that the variables removed were still insignificant when added back into the current preliminary main effects models, age, sex, race, marital, BMI group, and income were individually added back into the model. Results from the likelihood ratio test revealed that adding back in age was insignificant at the 0.05 level ($\chi^2(1)=0.77$, p=.0.38), as was sex ($\chi^2(1)=.01$, p=0.93), race ($\chi^2(1)=0.31$, p=0.58), and BMI group ($\chi^2(3)=7.88$, p=0.05). Marital status and income could not be compared via likelihood ratio test due to too many missing values.

Next, the beta coefficients from the univariate analysis were compared to the beta coefficients of the variables in the current preliminary main effects model. The coefficients did not change dramatically when CPY and education was included in the continuous exposure model and, therefore, we can conclude that the effect of each variable on AITD is not drastically attenuated when the other variables are included in the models.

Idiopathic Myxedema

Forward stepwise indicated that education, CPY, and BMI group helped predict IM case status while backward stepwise indicated that income additionally helped predict IM case status. After the Wald test, only BMI group and CPY remained in the model.

In order to ensure that the variables removed were still insignificant when added back into the current preliminary main effects model, age, sex, race, marital, education, and income, were individually added back into the model. Results from the likelihood ratio test (continuous exposure) revealed that adding back in age was insignificant at the 0.05 level ($\chi^2(1)=0.00$, p=.0.99), as was sex ($\chi^2(1)=.13$, p=0.72), and race ($\chi^2(1)=0.34$, p=0.56). Marital, education, and income could not be compared via likelihood ratio test due to too many missing values. This confirms that the original analysis' conclusion that age, sex, race, marital, educate, and income should not be included in the model was correct.

Next, the beta coefficients from the univariate analysis were compared to the beta coefficients of the variables in the current preliminary main effects model. None of the coefficients changed dramatically when the other variables are included in the model. Therefore we can conclude that the effect of each variable on Idiopathic Myxedema is not drastically attenuated when the other variables are included in the models.

Multivariate Analysis

All AITD Cases

To find the main effects model, the scale for continuous exposure and CPY was examined. To assess the linearity in the logit, a lowess curve of each continuous variable was performed.

The lowess curves revealed that continuous exposure did not have a very linear relationship with AITD cases and Gladder histograms by transformation plot indicated that a log transformation of the continuous exposure variable would be most useful. A Fractional Polynomial analysis confirmed that the untransformed continuous exposure variable was not linear.

After the J=2 model was compared to the linear model, it was confirmed that the linear model was a significantly worse fit (Linear: D= 1826.82, p= 0.55, J=1: D= 1825.56, p= 0.65). After the J=1 model was compared to the linear model, it was confirmed that the J=1 model was also a significantly worse fit (Linear: D= 1826.82, p= 0.26.) To find out if J=2 or J=1 model is better, we compared the results of the first fracpoly and found that the p-value was not significant (p= 0.65). Therefore there was no benefit to using the J=2 model over the J=1 model and so J=1 was used due to simplicity. Therefore, a log transformation of the continuous exposure variable is acceptable.

The transformed the continuous exposure variable was substituted for the non-transformed the continuous exposure variable into the model. After the transformation, the lowess curve appeared more linear and the fracpoly produced the largest p-value for linear meaning that the transformed continuous exposure variable is not significantly different than linear.

The lowess curves revealed that CPY did not have a very linear relationship with All AI Cases. However, because the continuous exposure variable was already being transformed, CPY was left untransformed to allow for more comprehensive interpretation.

In order to ensure that the current model ((log)continuous exposure, education and CPY) is the best model, the variables age, sex, BMI group and race were added back into the model individually to be sure they were still insignificant. The Likelihood ratio tests revealed that adding back in age was insignificant at the .05 level, as was sex, and race. After the log transformation, BMI group once again significantly improved the model at the α=.05 level and was added back into the main effects model, which then included ((log) continuous exposure), education, BMI group, and CPY.

A concern for this model was collinearity of the covariates because some of the covariates may to be associated with one another. If collinearity was present, it would lead to unreliable β coefficients. However, the Variance Inflation Factor (VIF) Approach of detecting collinearity did not identify any collinear variables (VIF<10).

Idiopathic Myxedema

To find the main effects model, the scale for continuous exposure and CPY was examined. To assess the linearity in the logit, a lowess curve of each continuous variable was performed.

The lowess curves revealed that the continuous exposure variable did not have a very linear relationship with Idiopathic Myxedema and Gladder histograms by transformation plot indicated that a log transformation of the continuous exposure variable would be most useful. A Fractional Polynomial analysis confirmed that the untransformed continuous exposure was not linear. After the J=2 model was compared to the linear model, it was confirmed that the linear model was a significantly worse fit (Linear: D=1775.13, p=0.649, J=1: D=1774.826, p= 0.510). After the J=1 model was compared to the linear model, it was confirmed that the J=1 model was also a significantly worse fit (Linear: D= 1775.126, p= 0.584

To find out if J=2 or J=1 model is better, we compared the results of the first fracpoly and found that the p-value was not significant (p= 0.510). Therefore there was no benefit to using the J=2 model over the J=1 model and so J=1 was used due to simplicity. Therefore, a log transformation of the continuous exposure variable is acceptable.

The transformed the continuous exposure variable was substituted for the non-transformed continuous exposure variable into the model. After the transformation, the lowess curve appeared more linear and the

fracpoly produced the largest p-value for linear meaning that the transformed continuous exposure variable is not significantly different than linear.

The lowess curves revealed that CPY did not have a very linear relationship with Idiopathic Myxedema. However, because the continuous exposure variable was already being transformed, CPY was left untransformed to allow for more comprehensive interpretation.

In order to ensure that the current model ((log)continuous exposure, CPY, and BMI group) is the best model, the variables age, sex, and race were added back into the model individually to be sure they were still insignificant. The Likelihood ratio tests revealed that adding back in age was insignificant at the .05 level, as was sex, and race. The main effects model included ((log) continuous exposure), CPY, and BMI group.

A concern for this model was collinearity of the covariates because as discussed in the introduction, some of the variables have been shown to be associated with one another. If collinearity was present, it would lead to unreliable β coefficients. However, the Variance Inflation Factor (VIF) Approach of detecting collinearity did not identify any collinear variables (VIF<10).

Model diagnostics

All AITD Cases

The goodness of fit, or the extent that the model predicts Idiopathic Myxedema, was assessed. A Pearson Residual test was conducted and it revealed that the number of covariate patterns was 2107. This was expected because when the logistic regression model contains one or more continuous covariates (continuous exposure and CPY), it is likely that the number of covariate patterns approximates the sample size (2107≈ 2115).

However, it is not appropriate to use Pearson Chi-Square test and/or Deviance based LRT because 1) there are 2 continuous variables in the model, and therefore, Hosmer-Lemeshow goodness of fit test was used to assess goodness of fit instead.

The HL test revealed that the model does not fit well because of the small p-value (X^2 (8)= 22.57, p=. 0.004). BMI group was removed from the model, which resulted in a much better fit for the model (X^2 (8)=9.30, p=0.32). Education was also dropped from the model because the model was a much better fit without it (X^2 (8)=6.42), p=0.60). Next the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were used

to compare the model with continuous exposure and the model with the transformed log(continuous exposure). For the model with continuous exposure (AIC= 1846.00, BIC= 1857.33), the AIC and BIC was larger than the model with log(continuous exposure) (AIC= 1832.912, BIC= 1849.11) meaning that the model with the log(continuous exposure) is slightly a better fit.

Next, the logistic regression was visually assessed for diagnostics using three plots: $\Delta Xj2\ vs.\pi\ j$, $\Delta Dj\ vs.\pi\ j$, and $\Delta\beta j\ vs.\pi\ j$. The points in the top left or top right corners identify covariate patterns that are poorly fit. No points were particularly suspicious. Next the plot of $\Delta Xj2\ vs.\ \pi j$ with symbol size proportional to $\Delta\beta j$ was examined to assess the size of the observations in the top left or right corners. No points were particularly suspicious.

Idiopathic Myxedema

The goodness of fit, or the extent that the model predicts Idiopathic Myxedema, was assessed. A Pearson Residual test was conducted and it revealed that the number of covariate patterns was 2105. This was expected because when the logistic regression model contains one or more continuous covariates (continuous explanatory variable and CPY), it is likely that the number of covariate patterns approximates the sample size (2105≈ 2127).

However, it is not appropriate to use Pearson Chi-Square test and/or Deviance based LRT because 1) there are 2 continuous variables in the model, 2) because J ≈ n, and 3) $X2$ and D do not follow $X^2_{J-(p+1)}$ under the null hypothesis when 1) and 2) are true. Therefore, Hosmer-Lemeshow goodness of fit test was used to assess goodness of fit instead.

The HL test revealed that the model fits well because of the large p-value (X^2 (8)= 2.83, p=. 0.94). Next the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were used to compare the model with continuous exposure and the model with the transformed log(continuous exposure). For the model with continuous exposure (AIC= 1787.13, BIC= 1821.10), the AIC and BIC were larger than the model with log(continuous exposure) (AIC= 1786.95, BIC= 1820.93) meaning that the model with the log(continuous exposure) is slightly a better fit.

Next, the logistic regression was visually assessed for diagnostics using three plots: $\Delta Xj2\ vs.\pi\ j$, $\Delta Dj\ vs.\pi\ j$, and $\Delta\beta j\ vs.\pi\ j$. The points in the top left or top right corners identify covariate patterns that are poorly

fit. No points were particularly suspicious. Next the plot of $\Delta Xj2\ vs.\ \pi j$ with symbol size proportional to $\Delta \beta j$ was examined to assess the size of the observations in the top left or right corners. No points were particularly suspicious.

Final model and interpretation

All AITD Cases

The final model includes log(continuous exposure) and CPY with 3 parameters.

$g(x) = logit(\pi(x))$ =βhat0 + βhat1*log(continuous exposure) + βhat2*CPY

$g(x) = logit(\pi(x))$ =-1.63 + -0.05*log(continuous exposure) + -0.01* CPY

The estimated OR for continuous exposure is 0.9544 suggesting that a 1 ug/m^3 increase in log(continuous exposure) is associated with a 4.56% decreased odds of AITD when controlling for CPY (95%CI: 0.89, 1.03).

The estimated OR for CPY is 0.9854 suggesting that a 1 year increase in CPY is associated with a 1.46% decrease in the predicted odd of AITD in the patient population, when controlling for continuous exposure (95%CI: 0.98, 0.99).

Final model for AITD, continuous exposure, and covariate

All AI Cases						
Variable	**β**	**95%CI, β**	**Std Error**	**OR**	**95% CI, OR**	**p**
Continuous Exposure	-0.05	-0.12, 0.03	0.04	0.95	0.89, 1.03	0.21
Cumulative Pack Years	-0.01	-0.02, -0.01	0.00	0.99	0.98, 0.99	<.01

Idiopathic Myxedema

The final model includes log(continuous exposure), CPY, and bmigrp with 6 parameters.

$g(x) = logit(\pi(x))$ =βhat0 + βhat1*log(continuous exposure) + βhat2* CPY + βhat3*bmigrp2 + βhat4*bmigrp3 + βhat5*bmigrp4

$g(x) = logit(\pi(x))$ =-1.90 + -0.04*log(continuous exposure) + -0.01* CPY + 0.85*bmigrp2 + 0.38*bmigrp3 + 0.31*bmigrp4

The estimated odds of Idiopathic Myxedema among underweight FMMP participants is 2.34 times more likely than participants with a normal BMI (95%CI: 0.90, 6.04) when continuous exposure and CPY are controlled. The estimated odds of Idiopathic Myxedema among overweight FMMP participants is 1.46 times more likely than participants with a normal BMI (95%CI: 1.09, 1.95) when continuous exposure and CPY are controlled. The

estimated odds of Idiopathic Myxedema among obese FMMP participants is 1.37 times more likely than participants with a normal BMI (95%CI: 1.01, 1.85) when continuous exposure and CPY are controlled.

The estimated OR for CPY is 0.986, suggesting that a 1 year increase in CPY is associated with a 1.38% decrease in the predicted odds of Idiopathic Myxedema in the patient population, when controlling for continuous exposure and BMI group (95%CI: 0.98, 0.99).

The estimated OR for continuous exposure is 0.96 suggesting that a 1 ug/m^3 increase in log(continuous exposure) is associated with a 3.79% decreased odds of Idiopathic Myxedema when controlling for CPY and BMI group (95%CI: 0.89, 1.04).

Final model for Idiopathic Myxedema, continuous exposure, and covariates

Idiopathic Myxedema						
Variable	**β**	**95%CI, β**	**Std Error**	**OR**	**95% CI, OR**	**p**
Continuous Explanatory	-0.04	-0.11, .04	0.04	0.96	0.89, 1.04	0.31
BMI group						
Normal	Reference	Reference	Reference	Reference	Reference	
Underweight	0.85	-0.10, 1.80	0.48	2.34	0.90, 6.04	0.08
Overweight	0.38	0.09, 0.07	0.15	1.46	1.09, 1.95	0.01
Obese	0.31	0.01, 0.62	0.16	1.37	1.01, 1.85	0.05
Cumulative Pack Years	-0.01	-0.02, -0.01	0.00	0.99	0.98, 0.99	<.01

B. Relationship between All Cases (all ICD-9 codes captured in case definition) and exposure (n=452)

Exposure		B	95%CI, B	Std Error	OR	95% CI, OR	p-value
Continuous Exposure (ug/m^3)		-0.10	-0.21, 0.02	0.06	0.91	0.81, 1.02	0.10
Log Continuous Exposure (ug/m^3)		-0.06	-0.12, 0.00	0.03	0.94	0.88, 1.00	0.06
Exposure Group							
	1	Reference	Reference	Reference	Reference	Reference	
	2	-0.05	-0.33, 0.23	0.14	0.95	0.72, 1.25	0.72
	3	-0.21	-0.44, 0.02	0.12	0.81	0.64, 1.02	0.08

C. Relationship between Initial Group 1 Cases (initially diagnosed as ICD-9 242.0) and exposure (n=12)

Exposure		B	95%CI, B	Std Error	OR	95% CI, OR	p-value
Continuous Exposure (ug/m^3)		-0.18	-0.88, 0.53	0.3612	0.8387	0.41, 1.70	0.63
Log Continuous Exposure (ug/m^3)		-0.23	-0.56, 0.10	0.1678	0.7927	0.57, 1.10	0.17
Exposure Group							
	1	Reference	Reference	Reference	Reference	Reference	
	2	-0.00	-1.36, 1.36	0.69	1.00	0.26, 3.89	1.00
	3	-1.08	-2.66, 0.49	0.80	0.34	0.07, 1.63	0.18

D. Relationship between Initial Group 2 Cases (initially diagnosed as ICD-9 242.8, 242.90, or 242.9) and exposure (n=147)

Exposure		B	95%CI, B	Std Error	OR	95% CI, OR	p-value
Continuous Exposure (ug/m^3)		-0.22	-0.44, -0.00	0.11	0.80	0.65, 1.00	0.05
Log Continuous Exposure (ug/m^3)		-0.10	-0.20 0.01	0.05	0.91	0.82, 1.01	0.07
Exposure Group							
	1	Reference	Reference	Reference	Reference	Reference	
	2	-0.21	-0.68, 0.25	0.24	0.81	0.51, 1.29	0.37
	3	-0.32	-0.70, 0.06	0.19	0.73	0.50, 1.06	0.10

E. Relationship between Initial Group 3 Cases (initially diagnosed as ICD-9 244.9) and exposure (n=285)

Exposure		B	95%CI, B	Std Error	OR	95% CI, OR	p-value
Continuous Exposure (ug/m^3)		-0.04	-0.18, 0.09	0.07	0.96	0.84, 1.10	0.53
Log Continuous Exposure (ug/m^3)		-0.03	-0.10, 0.05	0.04	0.97	0.90, 1.05	0.49
Exposure Group							
	1	Reference	Reference	Reference	Reference	Reference	
	2	0.02	-0.31, 0.36	0.17	1.02	0.73, 1.43	0.90
	3	-0.11	-0.40, 0.17	0.14	0.89	0.67, 1.18	0.43

F. Relationship between Initial Group 4 Cases (initially diagnosed as ICD-9 245.2 or 245.9) and exposure (n=8)

Exposure		B	95%CI, B	Std Error	OR	95% CI, OR	p-value
Continuous Exposure (ug/m^3)		-0.07	-0.85, 0.70	0.39	0.93	0.43, 2.02	0.86
Log Continuous Exposure (ug/m^3)		-0.31	-0.69, 0.07	0.20	0.73	0.50, 1.07	0.11
Exposure Group							
	1	Reference	Reference	Reference	Reference	Reference	
	2	0.15	-1.55, 1.86	0.87	1.17	0.21, 6.39	0.86
	3	-0.53	-2.23, 1.18	0.87	0.59	0.11, 3.24	0.55

G. Relationship between Initial Hyper Cases (initially diagnosed with a hyperthyroid ICD-9 code) and exposure (n=159)

Exposure		B	95%CI, B	Std Error	OR	95% CI, OR	p-value
Continuous Exposure (ug/m^3)		-0.21	-0.42, -0.01	0.11	0.81	0.66, 0.99	0.04
Log Continuous Exposure (ug/m^3)		-0.11	-0.21, -0.01	0.05	0.90	0.81, 0.99	0.03
Exposure Group							
	1	Reference	Reference	Reference	Reference	Reference	
	2	-0.19	-0.64, 0.25	0.23	0.82	0.53, 1.28	0.39
	3	-0.37	-0.74, 0.00	0.19	0.69	0.48, 1.00	0.05

H. Relationship between Initial Hypo Cases (initially diagnosed with a hypothyroid ICD-9 code) and exposure (n=293)

Exposure		B	95%CI, B	Std Error	OR	95% CI, OR	p-value
Continuous Exposure (ug/m^3)		-0.04	-0.18, 0.09	0.07	0.96	0.84, 1.09	0.52
Log Continuous Exposure (ug/m^3)		-0.04	-0.11, 0.04	0.04	0.97	0.89, 1.04	0.36
Exposure Group							
	1	Reference	Reference	Reference	Reference	Reference	
	2	0.03	-0.31, 0.36	0.17	1.03	0.74, 1.43	0.88
	3	-0.12	-0.40, 0.15	0.14	0.88	0.67, 1.17	0.38