Birthweight and risk of Autoimmune and Thyroid Conditions Within the Women’s Health Initiative

Brian c. Monahan

University of Massachusetts Amherst

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Birthweight and risk of Autoimmune and Thyroid Conditions Within the Women’s Health Initiative

A Thesis Presented

by

Brian C. Monahan

Submitted to the Graduate School of the University of Massachusetts Amherst in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

May 2021

Epidemiology
Birthweight and risk of Autoimmune and Thyroid Conditions Within the Women’s Health Initiative

A Thesis Presented

by

Brian C. Monahan

Approved as to style and content by:

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Cassandra Spracklen, Chair

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Susan Hankinson, Member

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Dr. Lisa Chasen Taber, Department Head
Department of Epidemiology and Biostatistics
DEDICATION

To Kathleen Cahill,
An inspiration, friend, and mentor
Gone but not forgotten.
ACKNOWLEDGMENTS

I would like to thank first and foremost Dr. Spracklen for her tireless effort and help in the editing, analyzing, and writing as well as being patient and kind throughout the entire process.

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Lastly, my friends I have made on this journey, thank you for keeping me on the right track and all the guidance we gave each other. The bonds and friendships will last a lifetime.
ABSTRACT
Birthweight and risk of Autoimmune and Thyroid Conditions Within the Women’s Health Initiative
MAY 2021

BRIAN C. MONAHAN, B.S, UNIVERSITY OF MAINE
M.S, UNIVERSITY OF MASSACHUSETTS AMHERST

Directed by: Professor Cassandra Spracklen

Autoimmune and thyroid conditions account for a substantial proportion of the morbidity and mortality experienced in the United States, affecting >40 million Americans combined. Co-occurrence of both an autoimmune and thyroid condition is also likely, particularly among women. Epidemiologic studies on both sets of conditions have examined many risk factors, including demographic, lifestyle, genetic, and environmental risk factors. However, one area which has been neglected is the effect of early life exposures on the development of autoimmune and thyroid conditions. To investigate the potential association between an individual’s birth weight (by category; <6lbs, 6-7lbs 15 oz, 8-9 lbs 15oz, ≥10lbs) and risk for autoimmune and thyroid conditions, we performed a nested case-control study among 76,087 multiethnic postpartum women in the Women’s Health Initiative (WHI) Observational cohort. Logistic regression models were used to estimate crude and adjusted odds ratios for associations between birth weight and: (1) autoimmune conditions (rheumatoid arthritis (RA), systemic lupus erythematosus (lupus), multiple sclerosis, type 1 diabetes, and ulcerative colitis/Crohn’s disease), and (2) thyroid conditions (hypothyroidism, hyperthyroidism, and goiter). After adjustments, birth weight was positively associated with odds for any thyroid condition (combined; P<0.02) and negatively associated with odds for hyperthyroidism (P=0.0002) within our prevalent model. Further, birth weight was significantly associated with hypothyroidism (P=0.0009) such that women weighing <6 lbs, 8-9.9 lbs, or ≥10lbs were at increased odds for hypothyroidism. No significant associations were observed between birth weight and any of the autoimmune conditions or goiter. Lupus (HR 1.51 [1.12, 2.03]) in all models and Hypothyroidism with the unadjusted model (HR 1.18 [1.05,1.31]) were also demonstrated to be at increased risk within the incident analysis. RA and Hypothyroidism produced no significant results within the Incident analysis. Our results further support the Developmental Origins of Health and Disease Hypothesis postulating that diseases that occur in childhood and later in life result from environmental exposures in utero and early childhood, extending the hypothesis to include thyroid conditions.
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1.1 Overview

Autoimmune conditions pose a significant health risk around the world. It is estimated that there are 14.7 million people living with an autoimmune condition in the US\(^1\). The prevalence of autoimmune disease is on the rise from 9 million people in 1997\(^2\) to 14.7 million people in 2012\(^1\). Common autoimmune conditions include type 1 diabetes (T1D), systemic lupus erythematosus (SLE), multiple sclerosis (MS), rheumatic arthritis (RA), ulcerative colitis (UC), and Crohn’s disease (CD).

Thyroid conditions have a burden similar in scale to autoimmune conditions. Currently there are an estimated 20 million Americans living with a thyroid condition. Thyroid conditions are classified into 4 main categories: underactive thyroid (hypothyroidism), overactive thyroid (hyperthyroidism), goiter, and thyroid nodules. The most common causes of thyroid conditions are cancers, autoimmune thyroid diseases (AITDs) such as Hashimoto’s thyroiditis and Graves’ disease, and iodine deficiencies. While not all thyroid conditions are autoimmune in nature, a bulk of autoimmune thyroid conditions are underdiagnosed as it is often easier to just manage the symptoms then diagnose the condition\(^3,4\).

Co-occurrence of both an autoimmune and thyroid condition is also likely, particularly among women\(^5-7\). It is estimated that 5-10\% of RA patients and 17-30\% of T1D patients will suffer from some sort of thyroid condition\(^8,9\). Further, thyroid, and autoimmune conditions share many common risk factors, including smoking, body mass index (BMI), age, ethnicity, and presence of an immune condition. By in large, however
the most consistent and major risk factors for autoimmune and thyroid conditions are family history and sex\textsuperscript{5,10–12}: Women bear most of the burden of both autoimmune and thyroid disease.

\textbf{1.2 Epidemiology: Autoimmune Conditions}

The immune system controls the body’s ability to eradicate and control infections from other pathogenic organisms, as well as assist in the repair process of other organ systems. The immune system functions through a variety of cell types and proteins that are made to recognize foreign invaders. Autoimmune conditions can result from the misregulation and/or mistargeting of the immune system which results in immune system recognizing the body as a foreign invader\textsuperscript{13}. As a group, each of the conditions are classified by autoantibody activity, or the presence of immune receptors that target one’s own body\textsuperscript{13–15}. These autoantibodies can affect different parts of the body, such as the pancreas (T1D)\textsuperscript{16}, joints (RA)\textsuperscript{17}, neurons (MS)\textsuperscript{18}, gastrointestinal system (UC/CD)\textsuperscript{19}, or just general cell surface receptors that are ubiquitous throughout the body (lupus)\textsuperscript{20}. While some autoimmune conditions, such as T1D, have very clear clinical presentation many others manifest with non-descript symptoms\textsuperscript{4}. For example, RA shares a lot of similar clinical symptoms with Osteoarthritis often leading to the underdiagnoses of Rheumatoid arthritis.

\textbf{1.2.1 Lupus}

Lupus is an autoimmune condition which targets a wide variety of body systems causing widespread inflammation and tissue damage in the joints, skin, lungs, kidneys, blood vessels, and brain\textsuperscript{21–24}. According to the Lupus Foundation of America, 1.5 million
Americans are estimated to be living with some form of lupus, 90% of which are women. Individuals are typically diagnosed with SLE between the ages of 15-44 and experience a variety of symptoms, such as skin rashes, fevers, joint pain/swelling, and fatigue. Persons afflicted with lupus are known to experience periods of “flare ups”, during which the individual may experience more severe symptoms or new symptoms that they may not have previously had. Flare ups can happen at any time, but are especially likely when a person with lupus is experiencing higher levels of emotional, mental, or physical stress.

Lupus can be deadly if left untreated. Early death as a result lupus is usually due to complications caused by infections, while death later in life is typically associated with atherosclerosis, or the buildup of fats on large to medium sized arterial walls. The increased risk for atherosclerosis in lupus patients has been demonstrated to be associated with high disease activity, treatments for the disease and other markers such as antiphospholipid antibodies. Treatments for lupus focus on managing symptoms and can vary widely based on the individual. Common treatments can include non-steroidal anti-inflammatory drugs (NSAIDs), antimalarials, corticosteroids, immunosuppressants, and monoclonal antibodies.

There are several known risk factors for the development of lupus. The most prevalent risk factor is sex: women are six times more likely to develop lupus than men. Additional prominent risk factors include minority racial and ethnic groups, age (15-44 years), and family history. Further, genome-wide association studies (GWAS) have identified >120 regions of the genome (“loci”) to be associated with an individual’s risk for lupus.
1.2.2 Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system \(^{30-32}\). MS is characterized by an exaggerated immune response to myelin, the compound that coats and insulates the neuron fibers \(^{30}\), resulting in communication problems between the brain and the rest of the body. Advanced stages of MS can even lead to permanent nerve damage, such as degradation of the axon itself \(^{30,31}\). It is estimated that 2.3 million people, globally, are living with MS. Diagnoses usually occur between 20-50 years of age with women bearing most of the burden of disease. Common symptoms of MS include: fatigue, vision problems, numbness, muscle spasm, mobility problems, and cognitive issues with thinking and mental health. \(^{30,31}\).

MS is a progressive disease meaning it will continue to worsen over the course of the person’s life \(^{18,33}\). Relapses, or periods of intense symptoms, usually occur rapidly, reaching a plateau that can last weeks until they subside \(^{18,33}\). Relapsing-remitting MS (RRMS) is the least severe and causes the least amount of complications. Within 15 years of the initial diagnosis, RRMS can develop into secondary progressive MS (SPMS), which is more severe. SPMS is characterized by its neurodegenerative complications: cognitive impairment and increasing severity of common MS symptoms \(^{18,33}\). The final form of MS is primary progressive MS (PPMS), which is characterized by a faster progression, more localized disease etiology, and more severe complications/symptoms, such as paraparesis and cognitive and progressive visual failure \(^{33}\). While treatments for MS are broad and specific to the individual \(^{18,30,33}\), there are two major strategies used: disease modifying treatments that reconstitute or suppress the immune system, and symptom-managing treatments \(^{18}\).
Risk factors for MS are similar to those of other autoimmune conditions\textsuperscript{2,31}. Age, female sex, geographical region, and racial or ethnic background are the most well-known and well-established risk factors\textsuperscript{32}. Specifically, women bear most of the burden of disease (74\% of cases)\textsuperscript{31}, and individuals of northern European-ancestry are diagnosed more frequently than those of other ancestries. There is also a positive association between MS and distance from the equator where those who live further from the equator have a higher risk for disease\textsuperscript{18,30}. Over 230 genetic variants have also demonstrated significant association with the risk for MS\textsuperscript{34}.

1.2.3 Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is a common autoimmune condition characterized by inflammation of the lining of the joints that can eventually result in bone erosion and/or joint deformity\textsuperscript{35–37}. In some individuals, RA can also damage the skin, eyes, lungs, heart, and blood vessels. RA is one of the most characterized autoimmune conditions, estimated to afflict 1.36 million people in the US with diagnoses starting as early as 30 years of age.

RA causes a variety of symptoms including tender or swollen joints, stiffness, fatigue, fever, and even loss of appetite\textsuperscript{36}. As mentioned above, RA does not have to affect only the joints but has been shown to cause complications with other body systems. These complications can range from minor effects such as mouth dryness to more serious inflammation of the cardiovascular system\textsuperscript{35–37}. The hallmark treatment for rheumatoid arthritis is the use of disease modifying antirheumatic drugs (DMARDs). Drugs included in the treatment of RA include: hydroxychloroquine, methotrexate, sulfasalazine, leflunomide, minocycline, azathioprine, cyclosporine, gold, cyclophosphamide,
antirheumatic biologic agents (i.e., tumor necrosis factor-α and interleukin 1 antagonists) 17,38–40.

Because RA is one of the more common autoimmune conditions 17,36,41, quite a bit is known about its epidemiology. Common risk factors for RA include age, smoking, higher BMI, and family history/genetic predisposition 37. There is also a large sex disparity: 75% of individuals diagnosed with RA are women 41. However, both fish and moderate alcohol consumption have been demonstrated to protect against RA development and symptom expression 37.

1.2.4 Type 1 Diabetes

Type 1 diabetes (T1D) is a chronic autoimmune condition in which the pancreas produces little to no insulin as a result of destruction or dysfunction of pancreatic beta cells 42,43. T1D has a global incidence of about 15 per 100,000 people. Within the US, the incidence is higher at 20 per 100,000 persons with a prevalence of 12.2 per 100,000 people. Unlike other autoimmune conditions, there is no difference in disease prevalence between sexes 43,44; however, there is a significant difference in mortality 45 with women being at a 40% greater risk of death.

There are several broad, moderate symptoms associated with T1D, ranging from frequent urination to extreme fatigue 46,47. However, there are several severe and/or life-threatening complications that can arise from mistreatment or lack of treatment, including diabetic ketoacidosis, neuropathy, glaucoma, cataracts, and various cardiovascular diseases such as high blood pressure and strokes 46,47. The most unique complication is diabetic ketoacidosis, which occurs when blood sugar levels are high, and ketones begin to build up within the blood stream. The primary treatment for T1D is insulin injection 47.
The other treatments include lifestyle changes, such as diet, blood sugar monitoring, and physical activity.

With the exact cause of T1D unknown, little is also known about the risk factors for T1D. Individuals with a family history of T1D are an increased risk for developing the disease; in fact, genetic studies have identified 80 loci associated with T1D, further illustrating the genetic nature of the condition. Other suggested risk factors for T1D include: white race, adolescent age, puberty; and environmental stressors such as entero-infections during pregnancy, Vitamin D deficiency, and intestinal microbiota. Unlike type 2 diabetes, diet and lifestyle habits are not associated with risk for T1D.

1.2.5 Ulcerative colitis/ Crohn’s disease

Ulcerative colitis (UC) and Crohn’s disease (CD) are autoimmune conditions of the gastrointestinal tract. While the two conditions are very similar in presentation and epidemiology, UC is continuous inflammation of the inner most layer of the colon whereas CD can occur anywhere along the digestive tract (from mouth to anus) with both inflamed and healthy tissues mixed together. Around 214 people out of 100,000 persons per year in the United states will be diagnosed with UC with CD being more rare at 3.1-20.2 per 100,000 individuals per year. Unlike many of the other autoimmune conditions previously mentioned, there is no sex discrepancy in prevalence rates of UC or CD.

Symptoms of both UC and CD include persistent and often bloody diarrhea, abdominal cramps/pain, and bowel urgency. While the conditions are limited to the gastrointestinal tract, complications of both conditions can affect a person’s overall health such as fevers, weight loss, low energy/fatigue, loss of appetite, anemia, and delayed
growth or development in children. There are many different treatments for UC/CD. According to The Chron’s and Colitis foundation, there are 30 FDA approved drugs across 5 classes. The medications as well as dietary changes are the main treatments for UC/CD. In some instances, an individual may undergo surgery to remove a heavily affected portion of the bowel, and the remaining ends are joined together.

The exact causes of UC and CD are unknown; however, both are much more common in individuals with a family history of either condition. Previously, diet and stress were suspected risk factors; research has now shown these factors may aggravate the condition and cause flare-ups but are not responsible for disease etiology. It is now believed that UC and CD are triggered by a malfunction in the immune system of those with a genetic susceptibility or predisposition for UC/CD. It has been suggested that an abnormal immune response to an invading virus or bacterium may cause the immune system to attack cells in the digestive tract as well, leading to UC/CD. In fact, there is a known association with the presence of Clostridium difficile and flare ups of both UC and CD. Nonetheless, the cause of the malfunctioning immune system or abnormal immune response is still to be determined.

1.3 Epidemiology: Thyroid Conditions

The thyroid is a small, butterfly-shaped endocrine gland that sits along the front of the windpipe. It has two lobes that are connected by the isthmus in the middle. The thyroid is primarily responsible for secreting two thyroid hormones—triiodothyronine (T₃) and thyroxine (T₄)—and a peptide hormone called calcitonin. T₃ and T₄ are responsible for maintaining the metabolic rate, cardiovascular function, sexual function, sleep patterns, and protein synthesis, as well as growth and development in children.
Calcitonin plays a role in calcium homeostasis. Thyroid hormone production in the thyroid is regulated by thyroid-stimulating hormone (TSH) released by the anterior pituitary gland. Clinically significant conditions of the thyroid include functional disorders (hyper- and hypothyroidism), as well as several diseases (e.g., nodules, goiter, Graves’ disease, Hashimoto’s thyroiditis, thyroid cancer). While not all thyroid conditions are autoimmune diseases, many have autoimmune etiologies. One of the leading causes of hyper- and hypothyroidism is Graves’ Disease and Hashimoto’s thyroiditis, respectively, both of which are autoimmune conditions. Goiter etiologies also include Graves’ disease and Hashimoto’s thyroiditis.

### 1.3.1 Hyperthyroidism

Overactive thyroid, or hyperthyroidism, occurs when the thyroid gland produces too much T₄, resulting in unintentional weight loss from an accelerated metabolism and a rapid and/or irregular heartbeat. In the US it is estimated that 1-3% of the population is living with overt hyperthyroidism. It can be caused by a number of conditions, including thyroiditis, thyroid nodules and Graves’ disease. Other symptoms of hyperthyroidism include: heart palpitations, fatigue, tremors, anxiety, heat intolerance, and disturbed sleep. Treatment for hyperthyroidism is highly dependent on the cause of hyperthyroidism. Medication against thyroid hormone production, radioactive iodine, and surgery are among the most common treatments for hyperthyroidism.

There are several known risk factors for hyperthyroidism. Women are affected more frequently than men, with an average onset between 40-60 years of age. Individuals are also at higher risk if they are of white race or of Japanese ancestry,
consume a diet high in saltwater fish and/or iodine, have an autoimmune condition, or have a family history of hyperthyroidism or Graves’ disease.\textsuperscript{58,69,73}.

1.3.2 Hypothyroidism

An underactive thyroid, or hypothyroidism, is a condition in which the thyroid gland does not produce enough thyroid hormone.\textsuperscript{59} Hypothyroidism is among the more common conditions of the thyroid in western countries with between 3-7\% of the US population having the condition.\textsuperscript{59} Hypothyroidism may be a result of a number of factors, including: Hashimoto’s thyroiditis or other autoimmune disease,\textsuperscript{63,74} over-response to hyperthyroidism treatment, thyroid surgery, radiation therapy, medications, a pituitary disorder, or an iodine deficiency. Cold and dry skin, brittle nails, bradycardia, delayed reactions, ataxia, fatigue, and elevated blood pressure are all common symptoms of an underactive thyroid.\textsuperscript{59,63} Untreated hypothyroidism can lead to several health problems, such as goiter, heart problems, mental health issues, neuropathies, myxedema, infertility, and birth defects.\textsuperscript{59} The primary treatment for hypothyroidism is levothyroxine, a synthetic form of thyroid stimulating hormone (TSH).

Epidemiological studies of hypothyroidism have identified several common risk factors for disease development. Like hyperthyroidism, women are more likely to develop hypothyroidism than men. Additional risk factors include: >60 years of age, family history of thyroid disease, presence of an autoimmune condition, history of treatment with radioactive iodine or anti-thyroid medications, history of radiation to the neck or upper chest, thyroid surgery, and having been pregnant or delivered a baby within the last six months.\textsuperscript{59}
1.3.3 Goiter

Goiter, or the enlargement of the thyroid, can be broken up into two main groups: diffuse and nodular goiter. While iodine deficiency is the most common cause of goiter worldwide, chronic autoimmune diseases, such as Hashimoto’s thyroiditis and Graves’ disease are the most common causes of goiter within the US. In the US it is estimated that 4.7% of the population is living with some form of goiter.

The symptoms of goiter can vary due to the different types and causes of the goiter. Goiters come in two forms toxic and non-toxic. Toxic goiter is characterized by increasing size of the thyroid partnered with the over production of the thyroid hormone thyroxine. Toxic goiter shares similar symptomology with hyperthyroidism, and, if left unchecked, can result in additional physical symptoms such as airway obstruction due to the large size of thyroid. Treatment options for toxic goiter typically include radioiodine therapy, antithyroid medication, and/or surgery. Non-toxic goiter are only characterized by increasing thyroid size but is not accompanied by hyperthyroidism. Non-toxic goiter can also be treated with radioiodine therapy, antithyroid medication, and/or surgery unless it is accompanied by hypothyroidism, in which case levothyroxine can be used in place of antithyroid medication.

Because goiters have multiple etiologies, complications vary based on the cause of the disease. However, there is one complication that is ubiquitous across goiter types: increased risk for thyroid cancer. Studies have shown that 10-20% of persons with a goiter will develop thyroid cancer. Further, if the goiter is allowed to grow in size, upper airway obstructions may become problematic and require surgical removal of the goiter.
Goiter does not have many independent risk factors. The most well researched risk factors for developing goiter are iodine deficiency\textsuperscript{61}, and autoimmune conditions, such as Hashimoto’s thyroiditis or Graves Disease\textsuperscript{3,76}.

1.4 Birthweight and the risk for autoimmune and thyroid conditions

The Developmental Origins of Health and Disease Hypothesis (DOHD), (also known as the “fetal origins hypothesis” or the “Barker Hypothesis”) is a hypothesis that postulates that chronic disorders or conditions in later life can result from environmental factors in utero (e.g., fetal malnutrition) and early childhood that permanently “program” the structure and function of systems within the body\textsuperscript{77}. The hypothesis, outlined by David Barker in “Fetal and Infant Origins of Adult Disease” (1992)\textsuperscript{78} has demonstrated an individual’s birth weight as a risk factor for many chronic diseases in both children and adults, such as autism\textsuperscript{79}, attention deficit/hyperactivity disorder\textsuperscript{80}, cardiovascular disease\textsuperscript{81}, type 2 diabetes\textsuperscript{82}, cancer\textsuperscript{83}, and later-life disability\textsuperscript{84}.

There is also evidence that prenatal factors, such as an individual’s birth weight, may influence the development of the immune system. Children born at low and high birth weights are at substantially increased risk for asthma\textsuperscript{85}. Further, children born at higher birth weights are at increased risk for allergic diseases, including eczema, food allergies, hay fever, and anaphylaxis\textsuperscript{86}. Although alterations of the immune system can persist into adulthood, the relationship of the DOHD and immune conditions remains elusive for select conditions. There are several conditions with limited or conflicting evidence while others like T1D are thoroughly examined.
1.5 Physiological Connection

Fetal insults in utero, including maternal and fetal exposures that result in infants born at both low (<2500 g) and high (≥ 4500 g) birth weights, have been shown to illicit epigenetic modifications of genes throughout the genome\textsuperscript{87}. These epigenetic mechanisms, which orchestrate fetal growth and development, may also remain “programmed” throughout an individual’s life, putting them at risk for later health consequences. In fact, several studies have demonstrated significant differences in patterns of DNA methylation by birth weight that have persisted past infancy\textsuperscript{88–90}. Further investigation is warranted to determine which epigenetic modification(s) may be most influential to the development of autoimmune and thyroid conditions.

Apart from epigenetic modifications, there is some evidence that birth weight may influence the development of the immune system. Infants born following intrauterine growth restriction (IUGR) have been found to have a global downregulation of the immune system, often associated with allergic disorders within children\textsuperscript{82}. Infants born IUGR and with low birth weights (<2500 grams) have also demonstrated a transient shift in T-cell and cytokine balance, altering systemic inflammatory responses\textsuperscript{91,92}. Additionally, low birth weight has been associated with low grade inflammation as well as several innate immune cells such as overall leukocytes, basophils, eosinophils and even platelets after adjusting for family history\textsuperscript{93}, and both inflammation and overactive immune responses are known to be risk factors for autoimmune conditions.

1.6 Study Objectives, Significance, and Innovation

This study proposes to assess the relationship between an individual’s weight at birth and risk for autoimmune (RA, MS, T1D, lupus, and UC/CD) and thyroid
(hypothyroidism, hyperthyroidism, and goiter) conditions. Specifically, the aims of the study are:

Aim 1: To assess the relationship between birth weight and the risk of autoimmune conditions such as rheumatoid arthritis, lupus, multiple sclerosis, ulcerative colitis, Crohn’s disease, and type 1 diabetes.

Hypothesis 1: We postulate that infants born at lower weights (< 6lbs) will be at an increased risk of developing autoimmune conditions overall.

Aim 2: To assess the relationship between birth weight and the risk of thyroid conditions such as hyperthyroidism, hypothyroidism, and goiter.

Hypothesis 2: We postulate that infants born at lower weights (< 6 lbs.) will be at an increased risk of developing thyroid conditions overall.

Because many autoimmune conditions are known to also affect the thyroid, it is common for individuals to have at least one autoimmune condition and a thyroid condition. This co-occurrence suggests a natural combination of the two sets of phenotypes. Studies relating birth weight to autoimmune and thyroid conditions are sparse and most have been conflicting. This study would be among the first to look at a large range of autoimmune and thyroid conditions within the same population rather than examine individual conditions in different populations. Further, the sample size and prospective design of the Women’s Health Initiative allows to analyze both prevalent and incident outcomes.
CHAPTER 2

METHODS

2.1 Women’s Health Initiative

The Women’s Health Initiative (WHI) is an ongoing prospective cohort study designed to study major causes of chronic disease in postmenopausal women. Briefly, 161,608 post-menopausal women aged 50-79 at enrollment were recruited from the general population at 40 US clinical recruitment sites between 1993-1998 \(^9^4\). Participants could have enrolled into overlapping clinical trials (WHI-CT; n = 67,932) or the long-term observational study (WHI-OS; n = 93,676). Detailed information about the WHI’s study design, recruitment, and implementation have been described elsewhere \(^9^4,9^5\). All study protocols were approved by the Institutional Review Board of each participating clinical center, and all participants provided written informed consent at study initiation.

2.2 Baseline Measures

Upon entry into the WHI-OS, all women completed structured, self-administered questionnaires to collect information on demographics; lifestyle factors; and medical, reproductive, and family history. Participants were asked to report their birth weight as one of the following categories: less than 6 pounds (lbs), 6 lbs to 7lbs 15ounces, 8 lbs to 9lbs 15 oz, and 10 or more lbs. The collection of birth weight is comparable to other studies of similar size and has been previously validated within those studies \(^9^6\). Women were also asked to report if they were born 4 or more weeks premature or were part of a multiple pregnancy (specifically, a twin or triplet). Further, a physical assessment was performed by trained staff to gather accurate measures of weight, height, and waist and
hip circumference at baseline. Participants were also asked to bring all current medications with them to the physical assessment.

2.3 Follow-up for outcome ascertainment

Clinical outcomes, including incident autoimmune and thyroid condition diagnoses, were reported by participants annually through in-person, mailed, and/or telephone questionnaires. In the third year of follow-up, women were invited to a follow-up clinical visit for an updated physical assessment. Like the assessment performed at baseline, the follow-up clinical visit was performed to gather updated anthropometric measures, as well as an updated list of current medications and other outcome information.

2.4 Outcome definitions and measurement

Data on prevalent thyroid and autoimmune conditions were obtained at baseline through the self-administered questionnaires. Women were first asked to report if a doctor had ever told them that they had a thyroid problem (yes/no/don’t know). If they answered yes, they were then asked a series of sub-questions (yes/no/don’t know) about specific thyroid conditions. We included the following thyroid conditions in our analyses: any thyroid gland problem, overactive thyroid, underactive thyroid, and goiter.

We included the following prevalent autoimmune conditions in our analyses: any autoimmune disease, type 1 diabetes (T1D), multiple sclerosis (MS), rheumatoid arthritis (RA), lupus (lupus), and Crohn’s disease/ulcerative colitis (CD/UC). We defined prevalent MS, lupus, and CD/UC as a self-report of a physician diagnosis of “multiple sclerosis”, “systemic erythematosus (‘lupus’ or SLE)”, or “ulcerative colitis or Crohn’s
"disease", respectively. Due to the lack of a specific variable for distinguishing those with type 1 and type 2 diabetes, we classified women as having T1D if they meet the following criteria reported at baseline: 1) self-reported physician diagnosis of ‘sugar diabetes when not pregnant; 2) reported the age of diabetes diagnosis < 30; and 3) reported using insulin as a treatment for their diabetes. Additionally, as the self-reported variable for RA has been poorly validated within WHI and often includes cases of osteoarthritis as shown in a previous study, we classified women as having prevalent RA if they simultaneously met the following criteria: 1) self-reported type of arthritis as “rheumatoid arthritis”; and 2) use of disease-modifying antirheumatic drugs (DMARDs).

Incident data were available for several of the thyroid and autoimmune conditions. Beginning in the third year of follow-up, women were asked to self-report any new lupus, RA, underactive thyroid, and/or overactive thyroid diagnoses that had occurred since the last completed survey. Women were considered as incident cases for each outcome if they responded “yes” to a recent diagnosis of lupus, underactive, and/or overactive thyroid. Like prevalent RA, women were required to indicate a recent diagnosis of RA and use DMARDs to be classified as an incident case of RA. Because medication coding only occurred in the third year of follow-up, our incident RA analyses were censored at the third year of follow-up.

2.5 Study Exclusion Criteria

For our analyses, women were excluded if they reported being born premature (n=7,282), reported being a twin or a triplet (n=1,616), or had a missing birth weight category (n=11,751). Women who had previously been diagnosed with a particular
condition prior to enrollment were excluded from the survival analyses for that same condition.

2.6 Statistical Analyses

Baseline characteristics of the study participants with and without any autoimmune or thyroid condition were examined using t-tests for continuous variables and chi-square tests for categorical variables. Logistic regression models were used to estimate odds ratios (OR) and their associated 95% confidence intervals (95% CI) between a woman’s birth weight and prevalent cases of autoimmune (any, RA, MS, lupus, T1D, and UC/CD) or thyroid (any, underactive, overactive, goiter) conditions with and without adjusting for potential risk factors. Cox proportional hazards regression models were used to estimate hazard ratios (HR) and 95% CI between a woman’s birth weight and incident cases of lupus, RA, underactive thyroid, and overactive thyroid with and without adjusting for potential risk factors. For birth weight, we used “6 lbs. to 7 lbs. 15 oz” as the referent category as infants born full-term within this weight range are considered to be of normal birth weight. Covariates selected for inclusion in our models are well-known risk factors for most autoimmune and/or thyroid conditions including age, race/ethnicity, region, BMI, smoking status, education, Normalized Socio-Economic Status (NSES), and alcohol use. All statistical tests were two-sided, and P-values <0.05 were considered statistically significant. Each outcome was considered independently with birth weight; therefore, we did not correct for multiple testing. For conservative interpretation, a Bonferroni-adjusted significance threshold of P<0.0035 (0.05/14) could be considered. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).
CHAPTER 3:
RESULTS

Results from the comparison of baseline characteristics are outlined in Table 1. Women with any autoimmune condition at baseline were more likely to be younger, identify as non-white, have a lower NSES, and have a lower BMI than women who did not report the presence of an autoimmune condition at baseline. Conversely, women who reported having any thyroid condition at baseline were more likely to be older, identify as white, and have a higher BMI, than women who did not report the presence of a thyroid condition at baseline.

Table 2 shows the crude and demographic- and lifestyle-adjusted odds of thyroid and autoimmune conditions by category of birth weight. Birth weight was significantly and positively associated with odds for any thyroid condition (all types combined) at baseline (unadjusted, P<0.0001). The association remained significant after adjustment for demographic (P=0.005) and lifestyle (P=0.02) factors, although the strength of the association was attenuated. A significant negative association was observed between birth weight and the odds for overactive thyroid (adjusted, P=0.009). Further, birth weight was significantly associated with underactive thyroid (adjusted, P=0.0002) such that women weighing <6 pounds, 8-9.9 pounds or ≥10 pounds at birth were at significantly increased odds for underactive thyroid. The magnitude of these associations is relatively modest ranging from fully adjusted OR’s of 1.14 (CI 1.02, 1.28) in the No significant associations were observed between birth weight and the odds for goiter, RA, MS, lupus, T1D, CD/UC, or any autoimmune disease (all types combined).
Crude and demographic- and lifestyle-adjusted hazards ratios of incident thyroid and autoimmune conditions are presented in Table 3. Women born in the highest birth weight category, >10 lbs, were at significantly increased risk for lupus in both crude (HR: 1.47, 95%CI 1.14-1.94) and adjusted models (demographic-adjusted, HR=1.43, 95% CI 1.08-1.90; demographic- and lifestyle-adjusted, HR=1.51, 95% CI 1.12-2.03) compared to women born weighting between 6 lbs – 7 lbs 15 oz. Women born weighing >10 lbs were also at significantly increased risk for underactive thyroid compared to women weighing 6 lbs – 7 lbs 15 oz at birth (unadjusted, HR=1.18, 95% CI 1.05-1.31); however, this association was attenuated after adjustments for covariates. No significant associations were detected within the incident models for overactive thyroid or RA.
Table 1: Baseline characteristics of 8,317 WHI Study participants, by autoimmune or thyroid condition status

<table>
<thead>
<tr>
<th>Condition</th>
<th>Any Autoimmune (n=1,419)</th>
<th>No Autoimmune (n=33,961)</th>
<th>P&lt;sub&gt;a&lt;/sub&gt;</th>
<th>Any Thyroid (n=18,958)</th>
<th>No Thyroid (n=56,475)</th>
<th>P&lt;sub&gt;b&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight</td>
<td>0.55 (68.4)</td>
<td>0.55 (68.4)</td>
<td>&lt;0.0001</td>
<td>0.55 (68.4)</td>
<td>0.55 (68.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age at baseline (mean, STD)</td>
<td>63.3 (7.0)</td>
<td>64.8 (7.1)</td>
<td>&lt;0.0001</td>
<td>64.2 (7.2)</td>
<td>63.0 (7.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1,175 (81.1)</td>
<td>29,143 (85.8)</td>
<td></td>
<td>16,992 (89.8)</td>
<td>47,276 (83.9)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>134 (11.0)</td>
<td>2,648 (8.0)</td>
<td></td>
<td>916 (4.8)</td>
<td>4,592 (8.2)</td>
<td></td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>29 (2.6)</td>
<td>593 (1.8)</td>
<td></td>
<td>303 (1.6)</td>
<td>1,534 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>54 (3.9)</td>
<td>987 (3.0)</td>
<td></td>
<td>432 (2.3)</td>
<td>2,119 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>24 (1.7)</td>
<td>493 (1.5)</td>
<td></td>
<td>272 (1.4)</td>
<td>802 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;High school diploma/GED</td>
<td>338 (22.8)</td>
<td>7,380 (22.0)</td>
<td></td>
<td>3,313 (17.6)</td>
<td>11,714 (20.9)</td>
<td></td>
</tr>
<tr>
<td>School after high school</td>
<td>699 (49.8)</td>
<td>16,413 (48.7)</td>
<td></td>
<td>9,120 (48.5)</td>
<td>27,156 (48.5)</td>
<td></td>
</tr>
<tr>
<td>College degree or higher</td>
<td>370 (27.3)</td>
<td>9,898 (29.3)</td>
<td></td>
<td>6,379 (33.9)</td>
<td>17,182 (30.7)</td>
<td></td>
</tr>
<tr>
<td>Normalized socioeconomic status (NSES; mean, STD)</td>
<td>74.9 (9.1)</td>
<td>75.8 (8.5)</td>
<td>&lt;0.0001</td>
<td>76.6 (7.9)</td>
<td>76.1 (8.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI at Baseline (mean, STD)</td>
<td>27.8 (6.3)</td>
<td>27.8 (6.3)</td>
<td></td>
<td>27.8 (6.3)</td>
<td>27.8 (6.3)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>414 (45.5)</td>
<td>16,884 (49.7)</td>
<td></td>
<td>8,971 (47.9)</td>
<td>28,551 (51.1)</td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>426 (46.8)</td>
<td>15,073 (44.3)</td>
<td></td>
<td>8,683 (46.4)</td>
<td>23,671 (42.4)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>70 (7.7)</td>
<td>2,039 (6.0)</td>
<td></td>
<td>1,067 (5.7)</td>
<td>3,618 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Alcohol use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Drinker</td>
<td>116 (12.7)</td>
<td>3,727 (10.9)</td>
<td></td>
<td>1,876 (10.0)</td>
<td>6,024 (10.7)</td>
<td></td>
</tr>
<tr>
<td>Past drinker/Average Drinker</td>
<td>572 (62.7)</td>
<td>17,928 (52.3)</td>
<td></td>
<td>9,866 (52.3)</td>
<td>27,794 (49.5)</td>
<td></td>
</tr>
<tr>
<td>Current drinker</td>
<td>225 (24.6)</td>
<td>12,625 (36.8)</td>
<td></td>
<td>7,119 (37.7)</td>
<td>22,372 (39.8)</td>
<td></td>
</tr>
<tr>
<td>Numbers are N (%) for categorical variables or mean (standard deviation) for continuous variables.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> p-values are from t-tests and Chi-square statistics and compare women with „any autoimmune“ condition to the women with „no autoimmune“ condition (among those used in this analysis).

<sup>b</sup> p-values are from t-tests and Chi-square statistics and compare women with „any thyroid“ condition to the women with „no thyroid“ condition (among those used in this analysis).
<table>
<thead>
<tr>
<th>Birth Weight Category</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6.5 lbs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.5-7.9 lbs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.0-9.9 lbs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10.0 lbs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Association of Birth Weight to Autonomic and Thyroid Conditions Among Women at the National Women's Health Initiative.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Unadjusted (cases = 555)</th>
<th>Adj for Demographics a (cases = 548)</th>
<th>Adj for Demographic and Lifestyle factors b (cases = 497)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rheumatoid arthritis</strong></td>
<td>1.17 [0.88, 1.56]</td>
<td>1.10 [0.82, 1.47]</td>
<td>1.03 [0.75, 1.41]</td>
</tr>
<tr>
<td><strong>Multiple sclerosis</strong></td>
<td>1.00 [Ref]</td>
<td>1.00 [Ref]</td>
<td>1.00 [Ref]</td>
</tr>
<tr>
<td><strong>Lupus</strong></td>
<td>0.99 [0.88, 1.56]</td>
<td>1.02 [0.82, 1.26]</td>
<td>0.98 [0.82, 1.24]</td>
</tr>
<tr>
<td><strong>Type 1 diabetes</strong></td>
<td>1.09 [0.72, 1.67]</td>
<td>1.19 [0.78, 1.82]</td>
<td>1.26 [0.82, 1.93]</td>
</tr>
<tr>
<td><strong>Ulcerative colitis</strong></td>
<td>0.71 [0.54, 1.15]</td>
<td>0.71 [0.54, 1.15]</td>
<td>0.76 [0.57, 1.07]</td>
</tr>
<tr>
<td><strong>Lupus</strong></td>
<td>1.10 [0.79, 1.57]</td>
<td>0.88 [0.68, 1.15]</td>
<td>0.89 [0.68, 1.16]</td>
</tr>
<tr>
<td><strong>Type 1 diabetes</strong></td>
<td>0.99 [0.88, 1.56]</td>
<td>0.99 [0.88, 1.56]</td>
<td>0.99 [0.69, 1.43]</td>
</tr>
<tr>
<td><strong>Multiple sclerosis</strong></td>
<td>1.17 [0.93, 1.47]</td>
<td>0.98 [0.83, 1.16]</td>
<td>0.97 [0.68, 1.40]</td>
</tr>
<tr>
<td><strong>Rheumatoid arthritis</strong></td>
<td>1.17 [0.93, 1.47]</td>
<td>0.97 [0.83, 1.16]</td>
<td>0.97 [0.66, 1.43]</td>
</tr>
<tr>
<td><strong>Multiple sclerosis</strong></td>
<td>1.19 [0.93, 1.52]</td>
<td>1.01 [0.86, 1.19]</td>
<td>0.97 [0.66, 1.43]</td>
</tr>
<tr>
<td><strong>Rheumatoid arthritis</strong></td>
<td>1.17 [0.93, 1.47]</td>
<td>1.01 [0.86, 1.19]</td>
<td>0.97 [0.66, 1.43]</td>
</tr>
<tr>
<td><strong>Multiple sclerosis</strong></td>
<td>1.19 [0.93, 1.52]</td>
<td>1.01 [0.86, 1.19]</td>
<td>0.97 [0.66, 1.43]</td>
</tr>
</tbody>
</table>

* T1D higher birthweight categories combined due to too few persons in the largest category.
Table 3: Relationship of birth weight to incident autoimmune and incident thyroid conditions among women in the Women’s Health Initiative.

<table>
<thead>
<tr>
<th>Birth Weight Category</th>
<th>Rheumatoid Arthritis (65 cases)</th>
<th>Autoimmune Conditions</th>
<th>Thyroid Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted (cases = 65)</td>
<td>adj for Demographics a (cases = 65)</td>
<td>adj for Demographics and Lifestyle factors b (cases = 93)</td>
</tr>
<tr>
<td>≥ 6 lbs</td>
<td>1.14 [1.00, 1.31]</td>
<td>1.05 [0.95, 1.16]</td>
<td>1.02 [0.81, 1.28]</td>
</tr>
<tr>
<td>6-7.9 lbs</td>
<td>1.00 [Ref]</td>
<td>0.99 [0.84, 1.16]</td>
<td>1.00 [Ref]</td>
</tr>
<tr>
<td>8-9.9 lbs</td>
<td>1.00 [Ref]</td>
<td>0.99 [0.84, 1.16]</td>
<td>1.00 [Ref]</td>
</tr>
<tr>
<td>≥ 10 lbs</td>
<td>1.00 [Ref]</td>
<td>0.99 [0.84, 1.16]</td>
<td>1.00 [Ref]</td>
</tr>
</tbody>
</table>

Policy from the Women’s Health Initiative will not allow researchers to report number of participants in cells less than 20. As such, cells that contain fewer than 20 participants read “<20”.

a Demographic factors include age, race, region, and BMI.
b Lifestyle factors include smoking status, education, normalized socioeconomic status, and alcohol use.

c Policy from the Women’s Health Initiative will not allow researchers to report number of participants in cells less than 20. As such, cells that contain fewer than 20 participants read “<20”.

dl for Demographic and Lifestyle factors (cases = 1,099)
edl for Demographic and Lifestyle factors (cases = 1,080)
CHAPTER 4

DISCUSSION

In the WHI, a well-established cohort of post-menopausal women, we found that women born within the heaviest birth weight category (>10 lbs) were at increased odds for underactive thyroid and decreased odds for overactive thyroid compared to women born at a normal birth weight. Further, the highest birth weight category was associated with increased risk for incident lupus compared to the normal birth weight category.

4.1 Comparison with prior literature

To our knowledge, the body of existing literature for the associations between birth weight and most autoimmune conditions is limited and inconsistent. Four studies were identified that examined the association between birth weight and RA, of which one found no association\textsuperscript{97}, one found individuals born with low birth weights to be at decreased odds for RA\textsuperscript{98}, and three studies found those born at higher birth weights to be at increased risk for RA\textsuperscript{96,99,100}. The study design most comparable to ours was performed within the Nurses’ Health Study (NHS)\textsuperscript{96}, a large nationwide prospective study. The analysis found an increased risk of RA at the highest birth weight category of >4.54 kg (RR 2.1 95% CI 1.2-3.6) compared to the normal birth weight category of 3.2-3.85 kg. While we found no association in our study between birth weight and RA, the NHS included a more thorough ascertainment of the RA outcome with medical chart abstraction conducted by trained rheumatologists\textsuperscript{96}. Even after validation with drug data, the RA variable used in the WHI study only reaches an estimated positive predictive value of 62.2%\textsuperscript{38}. 
We also identified four studies that previously examined the association between birth weight and lupus \textsuperscript{101–104}. Two studies found no association between birth weight and lupus when examining birth weight by category \textsuperscript{102} or as a continuous variable \textsuperscript{101}. One study performed within the national cohort, NIEHS Sister Study\textsuperscript{103}, identified low birth weight (<2,500 grams) to be significantly associated with the odds for lupus (OR 2.2, 95% CI 1.2–3.9) while another study with the NHS cohort identified high birth weight (≥10 lbs) to be associated with increased risk for lupus (RR 2.7, 95% CI 1.2–5.9) \textsuperscript{104}. The lupus results pose an interesting dilemma. In our prevalent data analysis, there was no significant association between lupus and any birthweight category in agreement with 2 of the previous studies \textsuperscript{101,102}. However, the incident data suggests a positive association with between higher birthweights and risk for lupus, agreeing with the NHS study \textsuperscript{104}. When we compare the outcome validation criteria for each study, our WHI study has the least stringent criteria.

Only three studies were identified that examined the association between birth weight and MS. Two studies found no association between birth weight and MS, including a longitudinal study conducted in Canada and a study performed within the NHS \textsuperscript{105,106}. Within the longitudinal Canadian study, birthweight was assessed as a continuous variable, and no association was detected with MS, even after stratification by sex (female P=0.48; male P=0.92). The analysis conducted within the NHS analyzed birth weight as a categorical variable \textsuperscript{106}. An additional case control study from Argentina found high birth weight (≥4kg) to increase the odds for MS in men (OR 6.58, 95% CI 4.81–8.99) and women (OR 4.5, 95% CI 3.06–6.58) \textsuperscript{107}. However, this study is
greatly limited by an unreliable population selection as well as a lack of transparent analysis, and therefore, is not internally valid.

There were two articles examining birthweight, among other early life factors, and risk of development of UC/CD\textsuperscript{108,109}. Both studies found no association between birth weight and incident cases of UC or CD. It is worth noting that both studies separated CD and UC into separate outcomes, while we were unable to do so due to the method of data collection within WHI. However, our results were consistent with these two prior studies.

In contrast to the other autoimmune conditions, a great deal of research has been done examining the association between birth weight and T1D. A meta-analysis\textsuperscript{110} looking at 29 studies predominantly within Europe demonstrated that children born at both 3.5 - 4 kg (OR 1.06 95% CI 1.01-1.11) and above 4kg (OR 1.10 95% CI 1.04-1.19) were at a higher risk for T1D. Out of the studies within the meta-analysis none of the studies focused on postmenopausal women. This result is further bolstered by several other studies conducted more recently\textsuperscript{111–113}. Our results depart from this previously explored relationship; however, our study had much lower power to detect an association, highlighted by our small number of cases (n<100) divided across four birth weight groups. This could be in large part to do with the population selected by WHI. Women collected by WHI must live long enough to become post-menopausal. T1D is known to become increasingly crippling as life goes on and might contribute to them being less likely to participate in a study such as this one. Additionally, T1D was never reported as its own variable within WHI and was collected in tandem with T2D. Due to the lack of T1D variable, a set of criteria had to be made that could ascertain T1D from T2D. This is
a large departure compared the other studies which used medical records from patient registries \(^{112,113}\), individual patient data \(^{110}\), and hospital statistics \(^{111}\). The lack of a validated T1D variable could have resulted in improper classification cases and could have been another reason that this study demonstrated a null result.

While the existing literature examining possible links between a person’s weight at birth and risk for autoimmune conditions is mostly limited, literature examining the impact of birth weight and thyroid conditions is even more scarce. We were able to locate one study that considered the association in twin pairs discordant for overt thyroid disease and found no associations between birth weight and autoimmune thyroid disease (Graves’ and Hashimoto’s thyroiditis) or non-autoimmune thyroid disease (simple goiter and toxic nodular goiter) \(^{114}\). However, we found women born weighing \(\geq 10\) lbs were at significantly increased odds of underactive thyroid and decreased odds for overactive thyroid. One possibility for this discrepancy is the use of twins. Twins were one of our exclusion criteria due to the presence of competition for resources within the gestational environment as well as twins being born at a significantly lower weight than single birth \(^{115}\). Another possibility is our substantially larger sample size, which afforded us sufficient power to detect the association. The discrepancy in results could be further explained by our broad assessment of thyroid conditions that does not specifically assess autoimmune thyroid conditions. Finally, the twin control study design of the existing study could be susceptible to overmatching, which could bias their results towards the null. Other studies have considered the relationship between birth weight and thyroid cancers \(^{64,116,117}\) and found a ubiquitous association with increased risk at higher birthweights.
4.2 Strengths & Limitations

This study has several key strengths. The WHI has a large sample size with extensive phenotype data collection at baseline. The prospective design of the WHI also allowed us to consider incident cases for four of our outcomes with up to 8 years of follow-up data available. We were also able to evaluate a broad spectrum of potential confounders that may account for the underlying association between birth weight and autoimmune or thyroid conditions.

Our study also has several limitations. First, our study was limited to evaluating categories of birth weight based on the woman’s self-report. While the most ideal birth data collection method would have been a quantitative measure obtained through medical records or birth certificates, self-reported birth weight by category has been shown to correlate well with medical record data in validity studies\textsuperscript{118,119}. Further, any bias that might result from potential misclassification of birth weight would be nondifferential.

Despite the large sample size of WHI, power remained a concern for most of the autoimmune outcomes. As stated above, the literature has demonstrated that extremely high birth weight is associated with increased risk for several autoimmune conditions. However, with <20 individuals within the high birthweight category half of the examined conditions, this relationship becomes difficult to detect with statistical significance. This lack of power increases the likelihood of a type 2 error or the acceptance of a false null hypothesis. The lack of power limited the secondary effect modification that would have been useful for conditions like lupus which is known to affect persons of color more than those of other races.
Birthweight is not the only variable that was collected in a self-reported categorical manner. All the outcomes along with some of the covariates were also recorded this way. While this has not been demonstrated to be of concern for the covariates it is a concern within some of the outcome variables. RA is one such variable with questionable validity within WHI. In a 2008 study validating the responses of the study in terms of secondary outcomes RA was found to be inaccurate \(^{38}\). The inaccuracy was theorized to result from confusion with osteoarthritis, which has a different etiology then RA. To increase the validity of the RA variable, we used medication data collected by WHI to validate if the subject was taking drugs indicative of RA \(^{38}\). The validation strategy was easy to implement for the RA baseline analysis but was more intricate when working with the incident data. Because medication data was only taken at baseline and 3 years after enrollment, it was impossible to validate any case that occurred after this 3\(^{rd}\) follow-up year. Due to this secondary limitation, it was decided that the follow-up of the incident RA cases would be artificially terminated at the time of the medication collection on the 3\(^{rd}\) year of follow-up. Another variable that was called into question in the same WHI validation study was lupus. However, upon analysis of the paper there was a much smaller group (total N=42; lupus cases=2) available for comparison, and the validity was indeterminate \(^{38}\).

Another limitation of this study is the lack of key covariates associated with these conditions. Familial history of these diseases is one such covariate. All the conditions have demonstrated that family history of the disease is a strong indicator for the development of the condition\(^{13,59,67}\). Another variable that is key for thyroid variables is the availability of iodine exposure data. The WHI did not collect information related to
iodine levels or consumption within the observational study participants. Iodine
deficiency has a large effect on thyroid conditions and is the most common cause of
thyroid conditions in poorer regions of the world \(^{59,65,72,120}\). However, because iodine
deficiency is thought to be a minor cause in more developed regions of the world,
including the US, we would not expect this potential confounder to have much influence
on our results.

Lastly the use of prevalent data comes with its own set of challenges and
limitations. Prevalent data often suffers from causal problems as both exposure and
outcome measured at the same point in time and therefore are usually hard to establish
that the exposure predates the outcome, and that the outcome does not predate the
exposure. For this study in particular this limitation is not of a concern as birth weight is
one of the earliest exposures available and therefore it is unlikely that outcome
supersedes our exposure of interest. The limitation of prevalent data is also circumvented
for select outcomes that were included in the incident analysis. In this instance we have
separation of exposure data collection and onset of disease and therefore can assume that
exposure superseded the disease occurrence.

4.3 Future Directions

Further research examining the associations between a person’s weight at birth
and subsequent risk for autoimmune and thyroid conditions is warranted. The existing
body of literature for all examined conditions (except for T1D) is very limited and
conflicting. While we were able to add to the body of evidence for many of the
conditions, our analyses were of limited power for detecting associations, particularly for
MS, lupus, and RA. In addition, we found significant associations between the highest
birth weight category and under- and over-active thyroid, results that now need to be replicated in additional populations. Further, we were unable to consider several potentially vital confounding variables, including family history of the conditions and iodine, nor were we able to consider potential racial disparities in the birth weight and autoimmune or thyroid condition relationship.
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