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Birthweight and subsequent risk for thyroid and autoimmune conditions in postmenopausal women

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Abstract

The objective of this study was to determine the association between birthweight and risk of thyroid and autoimmune conditions in a large sample of post-menopausal women. Baseline data from the Women's Health Initiative (n=80,806) were used to examine the associations between birthweight category (<6 lbs., 6–7 lbs. 15 oz, 8–9lbs. 15 oz, and ≥10 lbs.) and prevalent thyroid (underactive- and overactive thyroid and goiter) and autoimmune (lupus, rheumatoid arthritis, multiple sclerosis, ulcerative colitis/Crohn's disease) conditions. Follow-up questionnaire data were used to examine the associations between birthweight and incident underactive- and overactive thyroid, lupus, and rheumatoid arthritis. Logistic and Cox proportional hazards regression models were used to estimate crude and adjusted odds (OR) and hazards ratios (HR), respectively. Overall, women born weighing ≥10 lbs. had an increased risk for underactive thyroid [OR 1.14 (95% CI 1.02, 1.28)] and incident lupus [HR 1.51 (95% CI 1.12, 2.03)] and a decreased risk for overactive thyroid [OR 0.67 (95% CI 0.50, 0.92)] compared to women born weighing 6–7.99 lbs., after adjustment for adult BMI, demographic variables, and lifestyle factors. Further, women born weighing <6 lbs. were at increased risk for underactive thyroid [OR 1.13 (95% CI 1.04, 1.22)]. Birthweight was not associated with other thyroid or autoimmune disorders. High birthweight was associated with later-life thyroid and autoimmune conditions while low birthweight was associated with underactive thyroid. Preconception and prenatal interventions aimed at reducing the risk of both high and low birthweights may reduce the burden of later-life thyroid and autoimmune conditions.

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CONFLICTS OF INTEREST

None.

Keywords

birthweight; thyroid; autoimmune disease; lupus; rheumatoid arthritis; hyperthyroid; hypothyroid; postmenopausal women

INTRODUCTION

Autoimmune and thyroid conditions account for a substantial proportion of the morbidity and mortality in the United States.[1] Nearly 24 million Americans suffer from at least one autoimmune disease, such as lupus or rheumatoid arthritis (RA), and almost all autoimmune diseases are known to decrease life expectancy.[2] Additionally, an estimated 20 million Americans have some form of thyroid disease, the causes of which are often autoimmune in nature but not fully elucidated.[3,4] Co-occurrence of both an autoimmune and thyroid condition is also likely, particularly among women[5,6] who bear the bulk of the disease burden.[7] Epidemiologic studies on both sets of conditions have examined many risk factors, including demographic, lifestyle, genetic, and environmental risk factors.[8–10] However, one area that has been neglected is the association between early life exposures with risk of autoimmune and thyroid conditions.

The Developmental Origins of Health and Disease hypothesis, or “Barker hypothesis”, postulates that diseases arising in childhood and later in life result from exposure to environmental factors *in utero* and during early childhood.[11] The hypothesis has been frequently supported by chronic conditions that affect individuals later in life, such as cardiovascular disease, cancer, disability, and type 2 diabetes.[12–15] There is also evidence that prenatal factors may influence the development of the immune system and propensity to develop asthma and other allergic disorders in childhood.[16,17] Although alterations of the immune and endocrine system can persist into adulthood, few studies have considered the relationship between markers of early life growth and development and either adult onset-autoimmune or thyroid conditions that develop later in life.[18–21], especially given that endocrine transitions in women (i.e., puberty, pregnancy, and menopause) increase their susceptibility to autoimmune conditions.[22]

Thus, in the current study, we sought to investigate the potential associations between an individual’s birthweight and risk for: 1) thyroid conditions, including underactive thyroid, overactive thyroid, and goiter; and 2) autoimmune conditions, including rheumatoid arthritis (RA), lupus, multiple sclerosis (MS), ulcerative colitis (UC), and Crohn’s disease (CD). To evaluate the associations, we used the Women’s Health Initiative (WHI) Observational Study (OS), a well-characterized cohort of postmenopausal women.

METHODS

Study population

The 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 49–81 at enrollment and had a life-expectancy of at least 3 years were recruited from the general population at 40 US clinical recruitment sites between 1993–1998.[23,24] Participants

could have enrolled into overlapping clinical trials (WHI-CT; n=67,932) or the long-term observational study (WHI-OS; n=93,676). The analytic cohort for this study only included women in the WHI-OS. Detailed information about the WHI's study design, recruitment, and implementation have been described elsewhere.[23,25] 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.

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 histories. Participants were asked to report their birthweight as one of the following categories: <6 pounds (lbs), 6 lbs to 7lbs 15 ounces, 8 lbs to 9lbs 15 ounces, and ≥10 lbs. The collection of birthweight by category has previously been validated (Spearman r=0.75).[26] 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 anthropometric and other clinical measures at baseline. Participants were also asked to bring all current medications with them to the physical assessment.

Outcome definitions and measurement

Data on prevalent thyroid and autoimmune conditions were obtained at baseline through 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, MS, RA, lupus, and 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. 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[27], 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).

Clinical outcomes were reported by participants annually through in-person, mailed, and/or telephone questionnaires. 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. Similar to 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.

Exclusion criteria

For all of 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 were missing information on birthweight category (n=11,751). The final sample size for the case-control analysis was n≤80,806. Additionally, women who had reported at baseline that they had previously been diagnosed with lupus, RA, underactive thyroid, or overactive thyroid prior to enrollment were excluded from the Cox proportional hazards model for that same condition, resulting in a final sample size of n≤75,624.

Statistical analyses

Baseline characteristics of the study participants by birthweight category (< 6 lbs, 6 lbs to 7lbs 15 ounces, 8 lbs to 9lbs 15 ounces, and ≥10 lbs) 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 birthweight and prevalent autoimmune (any, RA, MS, lupus, and UC/CD) or thyroid (any, underactive, overactive, goiter) conditions. Cox proportional hazards regression models were used to estimate hazard ratios (HR) and 95% CI between a woman's birthweight and incident cases of lupus, RA, underactive thyroid, and overactive thyroid. For birthweight, 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 birthweight for female births between 1930–1950 in the United States.[28] Covariates selected for inclusion in our models were well-known risk factors for most autoimmune and/or thyroid conditions including age (continuous), race/ethnicity (categorical), region (categorical), BMI (continuous), smoking status (categorical)[29], education (categorical), neighborhood socio-economic status (NSES; continuous), and alcohol use (categorical). Because there is controversy in the field of life course epidemiology as to whether or not adult lifestyle factors, such as BMI, should be adjusted for in statistical models, we present results unadjusted, partially adjusted, and fully adjusted for demographic and lifestyle factors.[30,31] Because of prior associations between female hormones and both thyroid and autoimmune conditions[22,32], we additionally examined the use of female hormones (ever; yes/no) and pregnancy (ever been pregnant; yes/no) as covariates; however, inclusion of neither variable altered our results. All statistical tests were two-sided, and P-values <0.05 were considered statistically significant. Each outcome was considered independently with birthweight; therefore, we did not correct for multiple testing. For conservative interpretation, a Bonferroni-adjusted significance threshold of $p<0.0038$ (0.05/13) could be considered. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Results from the comparison of baseline characteristics are outlined in Table 1. Women born weighing <6 lbs. were more likely to be younger, have a lower NSES, identify as non-white,

be a current smoker, and have an autoimmune condition than women born weighing ≥6 lbs. Women born weighing ≥10 lbs. were more likely to be older and have a higher BMI at baseline than women born weighing <10 lbs. Characteristics of participants included in the survival analyses are provided in Supplemental Table 1.

Table 2 shows the crude and demographic- and lifestyle-adjusted odds of thyroid and autoimmune conditions by category of birthweight. Birthweight was significantly and positively associated with odds for any thyroid condition (all types combined) at baseline (unadjusted, p-value, test for linear trend <0.0001). The association remained statistically significant after adjustment for demographic (p-value, test for linear trend =0.005) and lifestyle (p-value, test for linear trend =0.02) factors, although the strength of the association was attenuated. Birthweight was associated with underactive thyroid in a U-shaped trend such that women weighing <6 lbs [OR 1.13, (95% CI 1.04, 1.22)], 8 lbs-9lbs 15 oz [OR 1.09, (95% CI 1.03, 1.15)], or ≥10 lbs [OR 1.14, (95% CI 1.02, 1.28)] at birth were all at increased odds for underactive thyroid. Further, a significant inverse association was observed between birthweight and the odds for overactive thyroid (adjusted, p-value test for linear trend=0.009) such that women born weighing <6 lbs had a 16% increase in odds [OR 1.16, (95% CI 0.99, 1.26)] and women born weighing ≥10 lbs had a 33% decrease in odds [OR 0.67 (95% CI 0.50, 0.92)] compared to women born between 6–7 lbs 15 oz. No significant associations were observed between birthweight and the odds for goiter, RA, MS, lupus, 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 birthweight category, >10 lbs, had a greater 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 weighing between 6 lbs–7 lbs 15 oz. Women born weighing >10 lbs also had a greater 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 associations were detected within the incident models for overactive thyroid or RA.

DISCUSSION

Within this large, well-characterized, nationwide cohort of post-menopausal women, we found that higher birthweight was associated with a higher risk for prevalent underactive thyroid and a lower risk for prevalent overactive thyroid. Further, women born in the highest birthweight category had a significantly higher risk for developing incident lupus compared to women born at a normal birthweight.

Previous studies examining the relationship between an individual's birthweight and risk for thyroid function and/or conditions are sparse. An infant's birthweight is related to their thyroid stimulating hormone (TSH) levels at birth[33,34], but this association does not appear to persist into childhood or adulthood[34,35]. Birthweight has also demonstrated inverse associations with free thyroxine (FT4) and triiodothyronine (T3) in older adult

twin pairs[35], as well as subclinical thyroid dysfunction and both thyroglobulin (TgAb) and thyroid peroxidase (TPOAb) autoantibodies[36,37], although a separate study found no association between birthweight and TgAB or TPOAb[38]. No associations were observed between birthweight and autoimmune (i.e. Grave's disease or Hashimoto's thyroiditis) or non-autoimmune (i.e. simple and toxic nodular goiter) thyroid diseases[18], however lower birthweights were shown to increase the risk for spontaneous hypothyroidism in older adults.[19] Moreover, low birthweight has consistently been associated with risk for congenital hypothyroidism[39,40], particularly transient congenital hypothyroidism.[40] Further, gestational diabetes, one of the leading causes of macrosomia (i.e. high birthweight), is an established risk factor for congenital hypothyroidism.[40,41] Consistent with the existing body of literature, results from our cross-sectional analysis indicate both low and high birthweights are associated with higher risk for underactive thyroid.

A small number of prior studies have considered the potential association between birthweight and each of the autoimmune conditions examined in this study. Among four studies considering birthweight as a risk factor for RA, one cohort study found no association[20] while three additional case-control and cross-sectional studies observed positive associations with birthweight.[42–44] Similarly for MS, one case-control and one cohort study found no association with birthweight[45,46] while a second case-control study found individuals born weighing ≥4kg were at increased odds for MS.[47] Results among studies examining risk factors for lupus are inconsistent with two case-control studies observing no association with birthweight[48,49], while a cohort study found a positive association[50] and a cross-sectional study found an inverse association with birthweight.[21] Lastly, two cohort studies found no associations between birthweight and either UC or CD.[51,52] Compared to our analyses, many of the aforementioned studies were conducted in populations of similarly aged or slightly younger women[20,43,45,50,51], including several from the Nurse's Health Study I and/or II.[20,45,50,51] While our cross-sectional results are consistent with those studies that found no association between birthweight and the various autoimmune conditions, our analyses are underpowered to find an association given the magnitude of association observed.

Because an individual's birthweight may be a marker for a variety of *in utero* exposures, determining the biological mechanism(s) by which birthweight influences the risk for thyroid and autoimmune conditions is complex.[53] Infants born at lower birthweights are at an higher risk for intrauterine growth restriction, resulting in hypothalamic-pituitary-thyroid (HPT) axis dysfunction.[54] Additional studies have suggested that fetal programming of the hypothalamic-pituitary-adrenal (HPA) axis may be one of the long-term changes that link low birthweight to adult disease, impacting cortisol responsiveness and, thus, chronic inflammation and autoimmunity.[54] In fact, adults with RA[55], lupus[56], and other autoimmune conditions[57,58] are known to have dysregulation of the HPA axis. At the other end of the growth spectrum, babies born weighing ≥10 lbs (i.e., fetal macrosomia) are more likely to be delivered by women who are obese, gain too much weight during pregnancy, or diagnosed with type 2 or gestational diabetes.[59] In conditions of fetal overnutrition, an imbalance of the appropriate set of nutrients needed for proper organ development results in the inability of the fetus to properly regulate its nutrient excess[60], potentially resulting in altered endocrine programming that could influence thyroid function.[61]

Strengths of our study include its large sample size with extensive phenotypic 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 birthweight and autoimmune or thyroid conditions.

Our study was limited to evaluating categories of birthweight based on 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 birthweight by category has been shown to correlate with medical record data in validity studies (58–87% correctly reported birthweight category).[62,63] Further, we hypothesize that any exposure misclassification would be nondifferential. Additionally, it is possible that women born within the normal birthweight range also experienced intrauterine growth restriction, a key event of fetal programming, which we would expect would bias our results toward the null.

There are also potential limitations related to our outcomes data. All of the outcomes evaluated in this study were self-reported without confirmation or adjudication, which would result in at least some misclassification. For example, the American Thyroid Association suggests that up to 60% of individuals with thyroid disease are unaware of their condition[64], which could result in a non-trivial number of women in our analyses being misclassified as controls. However, we would expect this underestimate the association and bias our results toward the null. Despite the large sample size of the WHI, the number of participants diagnosed with most of the rare autoimmune conditions was comparatively small, resulting in a lack of power, particularly for the lowest and highest birthweight categories. We were also unable to distinguish between clinically overt and subclinical under- and overactive thyroid, or between autoimmune or non-autoimmune causes, so our results may not generalize to all thyroid conditions.

Another limitation of our study was our inability to adjust for all of the covariates that may be particularly important in the pathophysiology of our examined conditions. For example, the WHI did not collect information related to iodine levels or iodine consumption in the observational study participants, and iodine deficiency is a well-known risk factor for thyroid dysfunction.[65] We also did not have data on other *in utero* pregnancy exposures, such as *in utero* tobacco smoking exposure, or other conditions relating to the pregnancy or mother's reproductive health, such as polycystic ovarian syndrome, preeclampsia, or gestational diabetes. Further, data on the participant's family history was only available for cardiovascular disease and related outcomes, cancer, and fracture history; no family history information was available for autoimmune or thyroid conditions.

In conclusion, we demonstrate that low birthweight (<6 lbs) may be associated with higher risk for underactive thyroid and higher birthweights (≥10 lbs) are associated with, 1) higher risk for underactive thyroid and incident lupus, and 2) lower risk for overactive thyroid. To our knowledge, this is the first study evaluating the association between birthweight and overactive thyroid, as well as the largest study conducted on the association between birthweight and underactive thyroid in adults. Our research provides additional evidence of the role of early developmental phenotypes in the development of later-life conditions,

further illustrating the importance of targeted interventions during preconception and prenatal care aimed at reducing both high and low birthweights and, thus, the burden of thyroid and autoimmune conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Baseline characteristics of 80,806 WHI study participants, by birthweight category

	< 6 lbs. (n=6,356)	6 lbs.−7 lbs. 15oz. (n=51,690)	8 lbs.−9 lbs. 15oz (n=15,405)	≥10 lbs. (n=2,636)	*P* [b]
Age at baseline (mean, STD)	62.9 (7.5)	63.3 (7.3)	63.4 (7.3)	65.0 (7.0)	<0.0001
Race/ethnicity					
White	4,590 (78.1)	43,802 (85.0)	13,694 (89.2)	2,232 (88.8)	<0.0001
Black	651 (10.3)	3,900 (7.6)	881 (5.7)	156 (8.2)	
Asian/Pacific islander	321 (5.1)	1,336 (2.6)	166 (1.1)	21 (2.7)	
Hispanic	306 (4.8)	1,790 (3.5)	419 (2.7)	70 (3.8)	
Other/unknown	111 (1.8)	735 (1.4)	198 (1.3)	47 (1.8)	
Education					
< High school diploma/GED	1,447 (22.9)	10,166 (19.8)	2,934 (19.2)	647 (24.8)	<0.0001
School after high school	3,069 (48.8)	24,855 (48.4)	7,370 (48.2)	1,288 (49.4)	
College degree or higher	1,778 (28.2)	16,303 (31.8)	4,975 (32.6)	672 (25.8)	
Normalized socioeconomic status (NSES; mean, STD)	75.3 (9.1)	76.3 (8.4)	76.4 (8.0)	75.4 (8.3)	<0.0001
BMI at baseline (mean, STD)	27.3 (6.0)	27.0 (5.7)	27.7 (6.1)	28.6 (6.6)	<0.0001
Smoking status					
Never	3,304 (52.8)	25,785 (50.5)	7,406 (48.7)	1,281 (49.4)	<0.0001
Past	2,509 (40.1)	22,124 (43.4)	6,815 (44.8)	1,144 (44.1)	
Current	447 (7.1)	3,115 (6.1)	993 (6.5)	171 (6.6)	
Alcohol use					
Non-drinker	833 (13.2)	5,350 (10.4)	1,485 (9.7)	310 (11.9)	<0.0001
Past drinker/average drinker	3,329 (52.7)	25,654 (49.9)	7,651 (50.0)	1,340 (51.2)	
Current drinker	2,155 (34.1)	20,381 (39.7)	6,173 (40.3)	965 (36.9)	
Any thyroid condition					
Yes	1,580 (24.9)	12,626 (24.4)	4,068 (26.4)	684 (25.9)	<0.0001
No	4,721 (74.3)	38,632 (74.7)	11,196 (73.6)	1,926 (74.1)	
Any autoimmune condition					
Yes	196 (3.1)	1,391 (2.7)	400 (2.6)	72 (2.7)	0.24
No	6,160 (96.9)	50,299 (97.3)	15,005 (97.4)	2,564 (97.3)	

Numbers are *N*(%) for categorical variables or mean (standard deviation) for continuous variables.

[a] 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 use in this analysis).

[b] 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 use in this analysis).

Table 2:

Association of birthweight to thyroid and autoimmune conditions among women at baseline in the Women's Health Initiative

	< 6 lbs. OR (95% CI)	6–7.99 lbs. OR (95% CI)	8–9.99 lbs. OR (95% CI)	≥ 10 lbs. OR (95% CI)	P_{trend}
n	9,569	53,537	15,709	2,702	
Thyroid conditions					
Any thyroid condition	1,580	12,626	4,068	684	
Unadjusted (cases=18,958)	1.02 (0.96, 1.09)	1.00 (Ref)	1.11 (1.07, 1.16)	1.08 (0.98, 1.18)	<0.0001
Adj for demographics[a] (cases=18,265)	1.07 (1.01, 1.14)	1.00 (Ref)	1.07 (1.02, 1.12)	0.99 (0.90, 1.08)	0.005
Adj for demographic and lifestyle factors[b] (cases=17,528)	1.09 (1.02, 1.16)	1.00 (Ref)	1.06 (1.01, 1.10)	1.03 (0.93, 1.14)	0.02
Underactive thyroid	992	7,820	2,668	455	
Unadjusted (cases=11,935)	1.04 (0.97, 1.12)	1.00 (Ref)	1.18 (1.12, 1.24)	1.18 (1.06, 1.31)	<0.0001
Adj for demographics[a] (cases=11,774)	1.09 (1.01, 1.17)	1.00 (Ref)	1.11 (1.05, 1.16)	1.05 (0.95, 1.16)	0.0002
Adj for demographic and lifestyle factors[b] (cases=10,245)	1.13 (1.04, 1.22)	1.00 (Ref)	1.09 (1.03, 1.15)	1.14 (1.02, 1.28)	0.0002
Overactive thyroid	209	1,467	456	51	
Unadjusted (cases=2,183)	1.16 (1.01, 1.35)	1.00 (Ref)	1.05 (0.94, 1.16)	0.68 (0.51, 0.90)	0.005
Adj for demographics[a] (cases=2,161)	1.15 (0.99, 1.34)	1.00 (Ref)	1.06 (0.95, 1.18)	0.67 (0.51, 0.90)	0.006
Adj for demographic and lifestyle factors[b] (cases=1,871)	1.16 (0.99, 1.36)	1.00 (Ref)	1.08 (0.96, 1.21)	0.67 (0.50, 0.92)	0.009
Goiter	199	1,520	500	81	
Unadjusted (cases=2,300)	1.07 (0.92, 1.24)	1.00 (Ref)	1.11 (1.00, 1.23)	1.05 (0.84, 1.32)	0.23
Adj for demographics[a] (cases=2,276)	1.07 (0.92, 1.24)	1.00 (Ref)	1.10 (0.99, 1.22)	1.02 (0.81, 1.28)	0.34
Adj for demographic and lifestyle factors[b] (cases=1,981)	1.05 (0.89, 1.23)	1.00 (Ref)	1.09 (0.97, 1.22)	1.03 (0.81, 1.31)	0.52
Autoimmune conditions					
Any autoimmune condition	196	1,391	400	72	
Unadjusted (cases=1,419)	1.15 (0.99, 1.34)	1.00 (Ref)	1.20 (1.00, 1.42)	1.13 (0.86, 1.49)	0.23
Adj for demographics[a] (cases=1,404)	1.15 (0.99, 1.34)	1.00 (Ref)	0.96 (0.86, 1.08)	1.01 (0.79, 1.29)	0.24

	< 6 lbs. OR (95% CI)	6–7.99 lbs. OR (95% CI)	8–9.99 lbs. OR (95% CI)	≥ 10 lbs. OR (95% CI)	P_{trend}
Adj for demographic and lifestyle factors[b] (cases=1,245)	1.13 (0.96, 1.33)	1.00 (Ref)	0.95 (0.84, 1.07)	1.03 (0.80, 1.32)	0.52
Rheumatoid arthritis	55	366	111	23	
Unadjusted (cases=555)	1.23 (0.92, 1.56)	1.00 (Ref)	1.02 (0.82, 1.26)	1.24 (0.81, 1.89)	0.60
Adj for demographics[a] (cases=548)	1.16 (0.87, 1.56)	1.00 (Ref)	1.02 (0.83, 1.27)	1.24 (0.81, 1.89)	0.60
Adj for demographic and lifestyle factors[b] (cases=497)	1.09 (0.80, 1.49)	1.00 (Ref)	0.99 (0.79, 1.25)	1.32 (0.86, 2.02)	0.60
Multiple sclerosis	<20	163	49	<20	
Unadjusted (cases=236)	0.85 (0.51, 1.40)	1.00 (Ref)	1.02 (0.73, 1.39)	0.84 (0.40, 1.80)	0.89
Adj for demographics[a] (cases=226)	0.90 (0.54, 1.48)	1.00 (Ref)	1.08 (0.79, 1.50)	0.87 (0.38, 1.97)	0.89
Adj for demographic and lifestyle factors[b] (cases=195)	0.92 (0.54, 1.57)	1.00 (Ref)	1.06 (0.75, 1.50)	0.82 (0.34, 2.01)	0.93
Lupus	37	270	71	<20	
Unadjusted (cases=391)	1.11 (0.79, 1.57)	1.00 (Ref)	0.88 (0.68, 1.15)	0.94 (0.54, 1.65)	0.68
Adj for demographics[a] (cases=338)	1.08 (0.77, 1.16)	1.00 (Ref)	0.89 (0.68, 1.16)	0.99 (0.57, 1.16)	0.78
Adj for demographic and lifestyle factors[b] (cases=335)	1.04 (0.72, 1.52)	1.00 (Ref)	0.88 (0.66, 1.17)	1.03 (0.57, 1.84)	0.82
Ulcerative colitis	86	611	184	31	
Unadjusted (cases=912)	1.15 (0.91, 1.44)	1.00 (Ref)	1.01 (0.86, 1.19)	0.99 (0.69, 1.43)	0.71
Adj for demographics[a] (cases=902)	1.17 (0.93, 1.47)	1.00 (Ref)	0.98 (0.83, 1.16)	0.97 (0.68, 1.40)	0.55
Adj for demographic and lifestyle factors[b] (cases=782)	1.19 (0.93, 1.52)	1.00 (Ref)	1.00 (0.83, 1.19)	0.97 (0.66, 1.43)	0.57

[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 with fewer than 20 individuals. As such, cells that contain fewer than 20 participants read "<20".

Table 3:

Association of birthweight to incident thyroid and autoimmune conditions among women in the Women's Health Initiative

	< 6 lbs. HR (95% CI)	6–7.99 lbs. HR (95% CI)	8–9.99 lbs. HR (95% CI)	≥ 10 lbs. HR (95% CI)	P_{trend}
n	6,001	49,484	14,774	2,493	
Thyroid conditions					
Underactive thyroid	590	4,713	1,387	269	
Unadjusted (cases=6,959)	1.05 (0.96, 1.14)	1.00 (Ref)	1.01 (0.95, 1.07)	1.18 (1.05, 1.31)	0.047
Adj for demographics[a] (cases=6,872)	1.08 (0.99, 1.18)	1.00 (Ref)	0.98 (0.93, 1.04)	1.11 (0.98, 1.25)	0.09
Adj for demographic and lifestyle factors[b] (cases=5,975)	1.05 (0.96, 1.16)	1.00 (Ref)	0.99 (0.93, 1.05)	1.12 (0.98, 1.27)	0.25
Overactive thyroid	233	1,698	469	90	
Unadjusted (cases=2,490)	1.14 (1.00, 1.31)	1.00 (Ref)	0.92 (0.83, 1.02)	1.06 (0.86, 1.31)	0.05
Adj for demographics[a] (cases=2,464)	1.13 (0.99, 1.33)	1.00 (Ref)	0.92 (0.83, 1.02)	1.02 (0.83, 1.27)	0.08
Adj for demographic and lifestyle factors[b] (cases=2,126)	1.10 (0.95, 1.28)	1.00 (Ref)	0.93 (0.84, 1.04)	1.01 (0.80, 1.26)	0.29
Autoimmune conditions					
Rheumatoid arthritis	<20	47	<20	<20	
Unadjusted (cases=65)	0.95 (0.38, 2.38)	1.00 (Ref)	0.84 (0.44, 1.57)	0.46 (0.06, 3.30)	0.83
Adj for demographics[a] (cases=65)	0.88 (0.35, 2.22)	1.00 (Ref)	0.87 (0.46, 1.64)	0.48 (0.07, 3.50)	0.87
Adj for demographic and lifestyle factors[b] (cases=57)	0.39 (0.09, 1.61)	1.00 (Ref)	0.86 (0.44, 1.68)	0.54 (0.07, 3.91)	0.55
Lupus	93	740	212	54	
Unadjusted (cases=1,099)	1.05 (0.84, 1.30)	1.00 (Ref)	0.95 (0.82, 1.11)	1.47 (1.14, 1.94)	0.04
Adj for demographics[a] (cases=1,080)	1.04 (0.84, 1.29)	1.00 (Ref)	0.96 (0.83, 1.12)	1.43 (1.08, 1.90)	0.07
Adj for demographic and lifestyle factors[b] (cases=930)	1.02 (0.81, 1.30)	1.00 (Ref)	0.97 (0.82, 1.14)	1.51 (1.12, 2.03)	0.04

[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 with fewer than 20 individuals. As such, cells that contain fewer than 20 participants read "<20".