

Childhood Weight Gain and Thyroid Autoimmunity at Age 60–64 Years: The 1946 British Birth Cohort Study

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Background: Complex bidirectional relationships have been described between body weight, thyroid function, and risk of thyroid disorders, including thyroid autoimmunity. We used a life-course approach to examine the potential association of childhood or adult body weight with the risk of thyroid autoimmunity and other thyroid disorders at age 60–64 years in a large population-based birth cohort study.

Methods: In the UK Medical Research Council 1946 British Birth Cohort study, at age 60–64 years, 1277 women and 1185 men (78% of the target sample) responded to a postal questionnaire, which included questions on thyroid disease and thyroid medication. Circulating antithyroid peroxidase antibodies, free T_4 , and TSH concentrations were measured in 1057 women and 997 men at a subsequent clinic visit. Birth weight was recorded, and height and weight were measured at ages 2, 4, 6, 7, 11, 15 years and also repeatedly in adulthood.

Results: At age 60–64 years, 10.9% of women (139 of 1277) and 2.3% of men (27 of 1185) reported they were taking T_4 , and 11.5% of women (122 of 1057) and 3.3% of men (33 of 997) had positive anti-TPO antibodies (>100 IU/mL), consistent with thyroid autoimmunity. Among women, both T_4 use and positive anti-TPO antibodies at age 60–64 years were positively associated with childhood body weight, childhood overweight, and adult body mass index. Childhood weight gain between 0 and 14 years of age was positively associated with later T_4 use (odds ratio 1.21, 95% confidence interval 1.03–1.42) and positive anti-TPO antibodies (1.21, 1.00–1.47). Women who were overweight or obese at age 14 years (127 of 972) had a higher risk of later positive anti-TPO antibodies (2.05, 1.12–3.76). In men and women without any thyroid disorders, serum free T_4 concentrations were inversely associated with concurrent body mass index ($P = .002$).

Conclusions: Childhood weight gain and childhood overweight conferred an increased susceptibility to later hypothyroidism and thyroid autoimmunity, particularly in women. (*J Clin Endocrinol Metab* 98: 1435–1442, 2013)

A complex bidirectional interrelationship between body weight and thyroid function is recognized (1). Thyroid hormones increase thermogenesis and energy expenditure, and overt hyperthyroidism typically leads to

weight loss and overt hypothyroidism leads to weight gain (2). There is also evidence for the opposite causal direction, ie, that changes in body weight may alter thyroid function. For example, in 1 study obese children had

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Abbreviations: anti-TPO, antithyroid peroxidase; BMI, body mass index; CI, confidence interval; CV, coefficient of variation; MS, multiple sclerosis; OR, odds ratio; SDS, SD score.

higher serum TSH and free T_3 concentrations than lean children, and these concentrations declined in those children who lost weight (3). Similarly, obese adults often have isolated hyperthyrotropinemia (4), and weight loss after gastric banding leads to a reduction in free T_3 and a rise in free T_4 concentrations (5).

However, findings from studies that compare thyroid function between obese and normal-weight individuals are inconsistent (6), and their findings often differ from those in the general population. For example, in 1 large population-based study, body mass index (BMI) was inversely associated with serum free T_4 concentrations (7), which is consistent with the expected physiological actions of T_4 on energy expenditure. This discordance between reports could be explained by the possibility that changes in weight can alter thyroid function through several different mechanisms (8). In addition to proposals that the adipocytokine leptin promotes TSH secretion (9) and that adiposity influences the activity of the deiodinase enzymes D1 and D2 resulting in a higher free T_3 to free T_4 ratio (5), a recent study reported that obese adults had a 2-fold higher risk of thyroid autoimmunity compared with normal-weight controls (10).

Thyroid autoimmunity has a complex pathogenesis. Various environmental determinants have been identified, including nutritional factors (11). For example, iodine overload, or even modest increases in iodine intake, increase the risk for thyroid autoimmunity and overt thyroid dysfunction (12). Of interest, the genetic susceptibility loci for thyroid autoimmunity include many immunoregulatory genes that confer susceptibility to other autoimmune diseases, such as type 1 diabetes, multiple sclerosis (MS), and rheumatoid arthritis (13), and such common disease pathways may explain the observed clustering of autoimmune diseases (14). Rapid weight gain and obesity may contribute to the pathogenesis of autoimmune disorders (15). A recent meta-analysis identified a consistent prospective association between childhood BMI and subsequent type 1 diabetes, with obese children having a 2-fold higher risk of diabetes (16). Similarly, in separate large US and Swedish studies, obese adolescents had a 2-fold higher risk of developing MS (17, 18). The association between obesity and thyroid autoimmunity has so far been described in only 1 cross-sectional study in adults (10).

To examine the prospective influences of childhood and adult body weight on the risk of hypothyroidism and thyroid autoimmunity, in a large UK birth cohort study, we collected data on the reported use of thyroid medication and measured circulating antithyroid peroxidase (anti-TPO) antibodies at age 60–64 years and related these values to weight, BMI, and height across the life course. We also measured circulating free T_4 and TSH concen-

trations at age 60–64 years and related these values to concurrent BMI.

Materials and Methods

Study design and data collection

The UK Medical Research Council National Survey of Health and Development is a prospective cohort of 2547 women and 2815 men, a socially stratified sample of all births that took place in England, Scotland, and Wales during 1 week in 1946 (19). Birth weight was extracted from medical records within 6 weeks of delivery, and heights and weights were measured by trained personnel at the ages of 2, 4, 6, 7, 11, 15, 36, 43, 53, and 60–64 years and were self-reported at the ages of 20 and 26 years. The study received Multi-Centre Research Ethics Committee approval, and written informed consent was given by the participants.

At age 60–64 years, 3163 participants were asked to complete a postal questionnaire, which included questions on thyroid disease and the use of thyroid medications (20). The remaining study members in the original cohort had died ($n = 717$), lived abroad ($n = 567$), had been untraced for more than 10 years ($n = 319$), or had previously withdrawn from the study ($n = 595$) (Stafford et al, manuscript under review). Of the target sample of 3163, 78% (1277 women and 1185 men) responded to this questionnaire; primary care physicians were subsequently contacted by questionnaire to validate positive self-reports of thyroid disease, including the age at first diagnosis. In instances in which there was missing age at first diagnosis of thyroid disease, responses were supplemented by similar information collected by nurse interview in 1999.

A fasting venous blood sample was collected at a research clinic or home visit at age 60–64 years on 2143 study members [75% of those sent invitations between 2 months and 2 years after the postal questionnaire (Stafford et al, manuscript under review)]. Thyroid function was analyzed at the Department of Clinical Biochemistry, Addenbrooke's Hospital, Cambridge, United Kingdom, according to the study's Duty of Care protocol (20). Serum TSH and free T_4 were measured by chemiluminescent immunoassay (Advia Centaur; Bayer Diagnostics, Newbury, United Kingdom). Any sample with abnormal values of free T_4 or TSH was also analyzed for free T_3 concentrations, by DELFIA (PerkinElmer, Buckinghamshire, United Kingdom) up to August 2009 and then by Advia Centaur using an analogous time-resolved fluorescence method. Circulating titers of thyroid peroxidase (TPO) antibodies were measured by chemiluminescent immunoassay (LUMI-test anti-TPO; Brahms, Berlin, Germany). For TSH, coefficients of variation (CVs) were 5.4%, 4.1%, and 4.3% at 0.5, 6.6, and 42.1 mIU/L, respectively. For free T_4 , CVs were 7.6% and 5.6% at 9.7 and 24.1 pmol/L, respectively. For free T_3 , CVs were 3.0% and 2.8% at 4.4 and 9.1 pmol/L, respectively. The manufacturer's normal range for TSH was 0.4–5.5 mIU/L and for free T_4 , 10–19.8 pmol/L. The normal range for free T_3 was 3.0–7.5 pmol/L for samples analyzed by DELFIA (PerkinElmer) and 3.5–6.5 pmol/L by Advia Centaur (Bayer). Positive anti-TPO antibodies were defined as values greater than 100 IU/mL.

Calculations

Among those study members without known thyroid disease, we identified previously unsuspected overt and subclinical thyroid dysfunction using the following established and reported criteria (21): 1) overt hyperthyroidism (low TSH with raised free T_4 and free T_3 or raised free T_3 alone); 2) subclinical hyperthyroidism (low TSH with normal free T_4 and free T_3); 3) euthyroid status (normal range TSH and free T_4); 4) subclinical hypothyroidism (high TSH with normal free T_4); or 5) overt hypothyroidism (high TSH with low free T_4).

BMI was calculated as weight (kilograms) divided by height squared (meters squared). Measures of BMI, weight, and height were converted into SD scores (SDS) using internally generated, sex-specific growth charts, which is preferable for historical cohorts, and were constructed using the LMS method (22). Overweight or obesity at age 14 years was defined as BMI greater than the 90th centile according to sex-specific internal references. Childhood weight gain between 0 and 14 years was calculated as weight SDS at 14 years minus weight SDS at birth.

Statistical analysis

Comparisons between groups were tested by χ^2 tests for categorical outcomes and ANOVA for continuous outcomes. Because of observed large differences in the prevalence of thyroid disorders between men and women, sex-specific analyses were performed to compare height, weight, BMI, and thyroid function test values between those with and without positive anti-TPO antibodies and the use of T_4 . Due to the very small numbers taking antithyroid medication (2 men and 3 women), we compared those taking T_4 with those not taking any thyroid medication. The odds ratios for thyroid disorders by childhood weight gain between 0 and 14 years and for childhood overweight or obesity at 14 years were calculated using logistic regression, separately by sex. Childhood weight gain was also adjusted for the intercepts (birth weight and height at 2 years) and for height gain at 2–14 years. In final logistic regression models for risk of thyroid disorders, childhood weight at 14 years was added to models that included adult weight or BMI at 60–64 years.

To investigate the potential physiological relationships between thyroid function and concurrent BMI, we restricted further analyses to those participants without any thyroid disorders (ie, those not taking any thyroid medication, with negative anti-TPO antibodies and being biochemically euthyroid). Normal-range free T_4 and TSH values were categorized into sex-specific quartiles, and these were related to BMI at 60–64 years using linear regression.

Results

Reported thyroid disorders

The use of T_4 at age 60–64 years was more common in women (10.9%; 139 of 1277) than in men (2.3%; 27 of 1185; χ^2 , $P < .0001$). A further 0.2% ($n = 3$) of women and 0.2% ($n = 2$) of men reported taking antithyroid medication. Of those participants whose primary care physicians provided information, use of T_4 to treat hypothyroidism was confirmed in 94 of 95 women (98.9%) and

Table 1. Body Size and Thyroid Function Test Results at Age 60–64 Years by Self-Reported Use of T_4 Medication

	No Thyroid Medication	Taking T_4	Student's <i>t</i> Test (<i>P</i> Value)
Women			
BMI, kg/m ²			
Mean	27.8 ± 5.3	28.9 ± 5.4	.04
n	947	110	
Weight, kg			
Mean	72.8 ± 14.7	75.9 ± 14.8	.03
n	948	110	
Height, cm			
Mean	1.62 ± 0.06	1.62 ± 0.06	.4
n	949	110	
Free T_4 , pmol/L			
Mean	14.4 ± 2.6	17.3 ± 3.5	<.001
n	876	102	
TSH, mIU/L			
Mean	3.1 ± 5.5	2.6 ± 3.6	<.001
n	874	102	
Men			
BMI, kg/m ²			
Mean	27.9 ± 4.1	26.9 ± 4.2	.3
n	940	21	
Weight, kg			
Mean	85.3 ± 13.5	83.1 ± 13.1	.4
n	940	22	
Height, cm			
Mean	1.75 ± 0.07	1.75 ± 0.08	.8
n	941	21	
Free T_4 , pmol/L			
Mean	14.6 ± 2.2	16.5 ± 3.4	<.001
n	892	20	
TSH, mIU/L			
Mean	2.3 ± 3.1	4.3 ± 10.5	.9
n	885	20	

Mean ± SD are displayed. These data exclude 3 women and 2 men who were taking antithyroid medication.

in 18 of 18 men (100%). Information on age at first diagnosis of hypothyroidism was available for 124 of 139 women and 23 of 27 men taking T_4 ; age at first diagnosis was younger than 20 years in 1 woman (at age 2 years), 20–30 years in 1 woman, and older than 30 years in the remainder.

Women who reported taking T_4 had higher body weight ($P = .03$) and higher BMI ($P = .04$; Table 1) at 60–64 years than women not taking any thyroid medication; in men no such differences were seen (both $P > .3$). Omission of the 1 woman with nonvalidated use of T_4 , and the 1 woman with a diagnosis of hypothyroidism before age 20 years did not substantially change the results (data not shown). When examining their previous body measurements, no differences were seen with birth weight ($P = .6$), but women taking T_4 had higher body weights at ages 6, 7, 11, 15, 20, 26, 36, and 53 years and higher BMI at ages 11, 15, 20, 36, and 53 years, compared with other women (Figure 1) (see Supplemental Table 1, published on

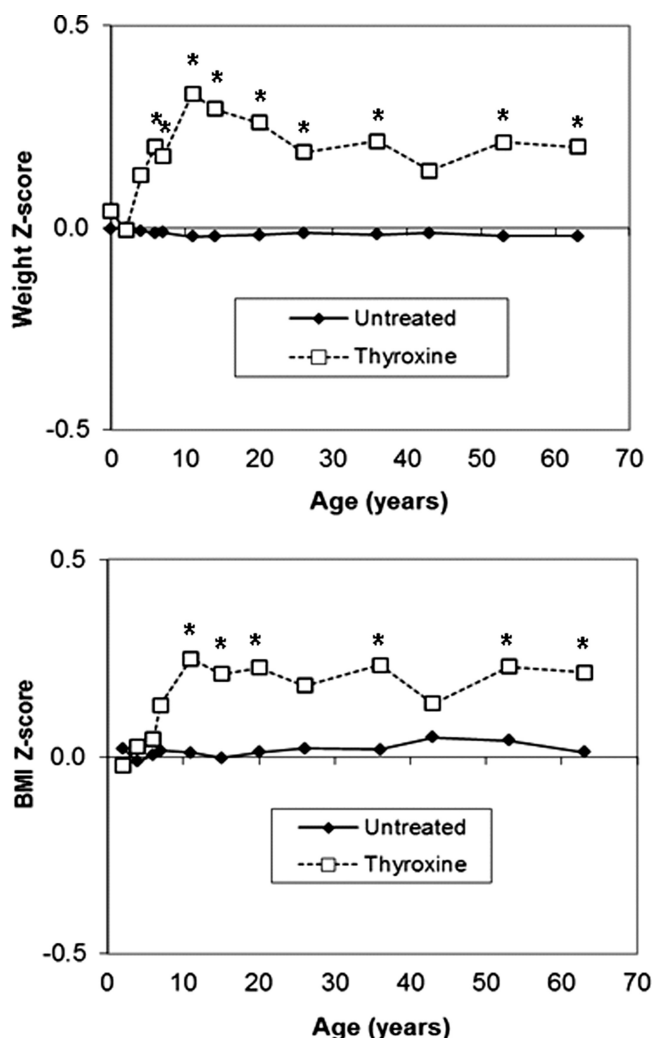


Figure 1. Mean weight and BMI Z-scores from birth to age 60–64 years in women taking T_4 and untreated women. * $P < .05$.

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Women taking T_4 had higher circulating free T_4 concentrations and lower TSH concentrations than untreated women (Table 1), which reduces the likelihood of inadequate thyroid replacement as a cause of their higher body weight and BMI.

Thyroid autoimmunity

At age 60–64 years, the prevalence of positive anti-TPO antibodies (>100 IU/mL) was more common in women (11.5%; 122 of 1057) than in men (3.3%; 33 of 997; $P < .0001$). Among those taking T_4 , the prevalence of positive anti-TPO antibodies was similar in women (38.6%; 39 of 101) and in men (35.0%; 7 of 20). Accordingly, among those with positive anti-TPO antibodies, the prevalence of T_4 use was similar in women (32.0%; 39 of 122) and in men (21.2%; 7 of 33).

Women with positive anti-TPO antibodies had higher body weight ($P = .04$) and tended to have higher BMI ($P =$

.08) than other women; in men no such differences were seen (Table 2). Similar trends to higher BMI and body weight by anti-TPO antibody positivity were seen among those women not taking any thyroid medication (BMI: $P = .07$; weight: $P = .02$, data not shown). When examining their previous body measurements, no differences were seen with birth weight ($P = .7$), but women with positive anti-TPO antibodies had higher body weights at ages 2, 4, 6, 7, 15, 20, 36, and 53 years and higher BMI at age 14 years (Figure 2 and Supplemental Table 2).

Among those not taking any thyroid medication, men and women with positive anti-TPO antibodies had lower serum free T_4 and higher TSH concentrations than those with negative anti-TPO antibodies (Table 2).

Childhood weight gain and overweight

Independent of childhood height gain, each +1 SDS in childhood weight gain between 0 and 14 years was asso-

Table 2. Body Size and Thyroid Function Test Results at Age 60–64 Years by Anti-TPO Antibody Levels

	Anti TPO <100 IU/mL	Anti TPO >100 IU/mL	Student's t Test (P Value)
Women			
BMI, kg/m ²			
Mean	27.7 ± 5.2	28.5 ± 5.7	.08
N	931	122	
Weight, kg			
Mean	72.4 ± 14.5	75.3 ± 15.6	.04
N	932	122	
Height, cm			
Mean	1.62 ± 0.06	1.62 ± 0.06	.2
N	933	122	
Free T_4 , pmol/L ^a			
Mean	14.5 ± 2.2	13.8 ± 6.0	.01
N	870	83	
TSH, mIU/L ^a			
Mean	2.6 ± 2.2	7.8 ± 16.0	<.001
N	869	82	
Men			
BMI, kg/m ²			
Mean	27.9 ± 4.1	28.0 ± 4.8	.9
N	959	33	
Weight, kg			
Mean	85.3 ± 13.4	86.5 ± 15.1	.6
N	959	33	
Height, cm			
Mean	1.75 ± 0.07	1.76 ± 0.06	.4
N	960	33	
Free T_4 , pmol/L ^a			
Mean	14.6 ± 2.2	12.8 ± 2.6	<.001
N	948	26	
TSH, mIU/L ^a			
Mean	2.1 ± 1.2	7.8 ± 15.8	<.001
n	941	26	

Mean ± SD are displayed. Anti-TPO antibody levels greater than 100 IU/mL were taken as indicative of thyroid autoimmunity.

^a Free T_4 and TSH analyses were restricted to study members not taking thyroid medications.

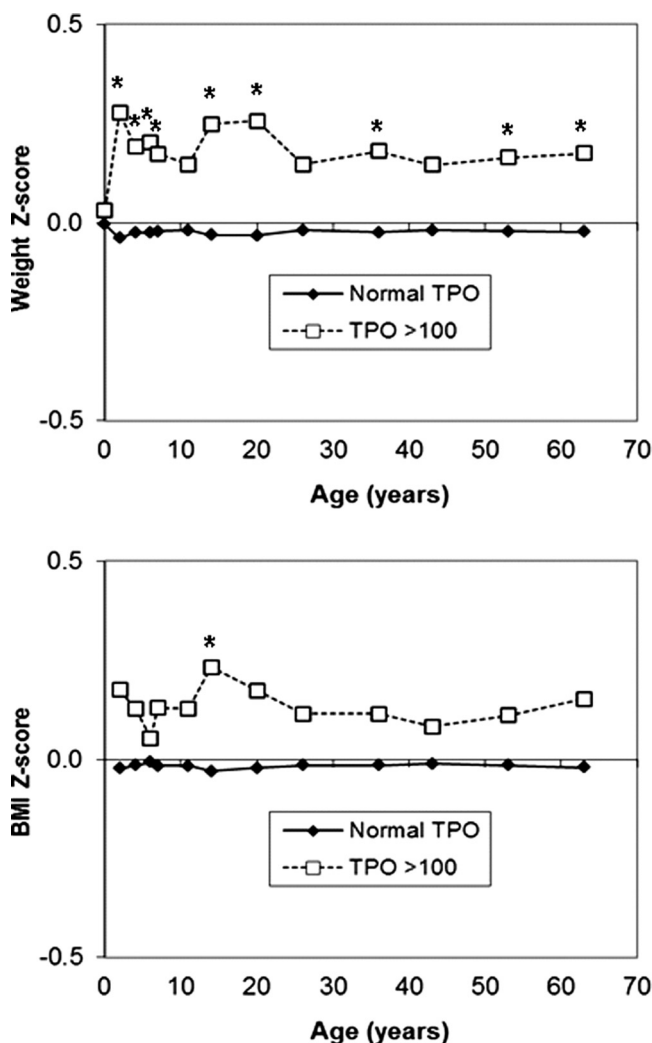


Figure 2. Mean weight and BMI Z-scores from birth to age 60–64 years in women with high (>100 IU/mL) vs negative anti-TPO antibodies. * $P < .05$.

ciated with higher risks for T_4 use [odds ratio (OR) 1.42, 95% confidence interval (CI) 1.09–1.84] and positive anti-TPO antibodies (OR 1.71, 95% CI 1.23–2.37) at 60–64 years in women but not in men (Table 3). Accordingly, women who were overweight or obese at age 14 years (127 of 972) had a trend to higher risk for T_4 use (OR 1.36, 95% CI 0.80–2.31) and a higher risk of positive anti-TPO antibodies (OR 2.05, 95% CI 1.12–3.76). Men who were overweight or obese at age 14 years (137 of 924) had a higher risk of T_4 use at 60–64 years (OR 3.50, 95% CI 1.16–10.61) but no difference in risk of positive anti-TPO antibodies (OR 1.16, 95% CI 0.38–3.51) (Table 3). After adjustment for childhood weight at age 14 years, adult weight and BMI at 60–64 years were no longer associated with T_4 use or positive anti-TPO antibodies in men or women (all $P > .1$, data not shown).

Thyroid function tests

At age 60–64 years, thyroid function test values were used to categorize study subjects not taking any thyroid

Table 3. Odds Ratios for Thyroid Disorders in Men and Women at Age 60–64 Years by Childhood Weight Gain, Height Gain and Weight Status at Age 14 Years

	Women	Men
Use of thyroxine		
Weight gain 0–14 y ^a	1.42, 1.09–1.84	1.32, 0.60–2.86
Height gain 2–14 y ^a	1.07, 0.82–1.41	0.98, 0.45–2.11
Overweight or Obese at 14 y ^b	1.36, 0.80–2.31	3.50, 1.16–10.61
High anti-TPO antibodies (>100 IU/mL)		
Weight gain 0–14 y ^a	1.71, 1.23–2.37	0.97, 0.46–2.03
Height gain 2–14 y ^a	1.00, 0.73–1.39	1.17, 0.57–2.40
Overweight or Obese at 14 y ^b	2.05, 1.12–3.76	1.16, 0.38–3.51

Statistically significant ($P < .05$) associations are highlighted in bold type.

^a Odds ratios (95% CI) are shown per +1 U gain in weight SDS between 0–14 yr, and per +1 U gain in height SDS between 2–14 yr. Models included both weight gain and height gain, and were also adjusted for birth weight SDS and height SDS at age 2 yr.

^b Odds ratios (95% CI) are shown for overweight or obesity at age 14 yr (defined as BMI >90th centile according to sex-specific internal references) vs. all others.

medication into categories of previously unsuspected overt or subclinical thyroid dysfunction using established criteria (Table 4) (21). Fewer women (91.1%; 874 of 959) were categorized as biochemically euthyroid than men (97.5%; 953 of 977). Having positive anti-TPO antibodies was associated with a higher risk of overt or subclinical hypothyroidism in women (OR 8.6, 95% CI 5.0–14.9) and in men (OR 21.3, 95% CI 7.3–61.7).

Among those men ($n = 906$) and women ($n = 806$) without any thyroid disorders (ie, not taking any thyroid medication, negative anti-TPO antibodies, and euthyroid thyroid function test values), higher free T_4 quartile was associated with lower concurrent BMI (linear trend, $P = .002$, adjusted for sex; Figure 3). Within each sex, those in the highest free T_4 quartile had lower BMI than those in any of the 3 lower quartiles (mean $\pm$ SD in women, 26.8 $\pm$

Table 4. Prevalence of Undiagnosed Thyroid Disorders at Age 60–64 Years By Sex

Category ^a	Women	Men	Total
Overt hyperthyroidism	4 (0.4%)	1 (0.1%)	5 (0.3%)
Subclinical hyperthyroidism	7 (0.7%)	4 (0.4%)	11 (0.6%)
Euthyroid	874 (91.1%)	953 (97.5%)	1827 (94.4%)
Subclinical hypothyroidism	65 (6.8%)	18 (1.8%)	83 (4.3%)
Overt hypothyroidism	9 (0.9%)	1 (0.1%)	10 (0.5%)
Total	959	977	1936

^a Based on categories described by Wilson et al (21).

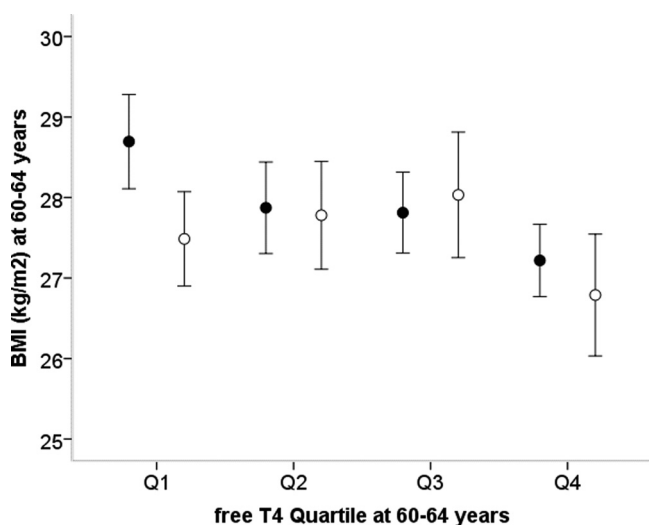


Figure 3. Mean $\pm$ 95% confidence intervals for BMI at age 60–64 years by quartiles of circulating free T_4 concentration in women (open circles) and men (solid circles) without any thyroid disorders.

5.4 vs 27.7 ± 5.1 kg/m²; $P = .03$; in men, 27.3 ± 3.4 vs 28.2 ± 4.3 , $P = .004$).

There was no association between TSH quartile and concurrent BMI in women (linear trend, $P = .3$) or in men (linear trend, $P = .6$) separately or combined (linear trend, $P = .3$, adjusted for sex).

Discussion

In a large prospective birth cohort study, we found evidence for both pathological and physiological links between body weight and thyroid function. Women taking T_4 and women with positive anti-TPO antibodies at age 60–64 years were heavier as children and as adults than other women, they had faster weight gain in childhood independent of height gain, and they were more likely to have been overweight or obese as children. Separately, in men and women without any detectable thyroid disorders, we identified an inverse relationship between serum free T_4 concentrations and concurrent BMI, which is consistent with previous studies (7) and also consistent with the expected physiological influence of T_4 on energy expenditure (2).

Strengths and limitations

The main strengths of the study are its representative nature and its long-term prospective design, which allowed robust assessment of the timing of childhood weight gain on later thyroid outcomes. Furthermore, we found consistent associations between childhood weight status or weight gain and both self-reported T_4 use and objectively assessed thyroid antibody status.

Limitations of our study include the lack of measures of thyroid autoantibodies or thyroid function prior to 60–64 years. Autoimmune hypothyroidism is the most common cause of hypothyroidism in this age group in the United Kingdom (23), yet less than 40% of study members taking T_4 had positive anti-TPO antibodies, probably reflecting the decline in thyroid antibody titers after T_4 treatment and time from diagnosis (24). Repeated measures of anti-TPO antibody levels during adult life may have confirmed more study members with thyroid autoimmunity but whose antibody levels regressed spontaneously or after T_4 treatment. Further follow-up measurements would also have allowed us to assess the prospective influence of free T_4 and TSH concentrations on adult body weight. T_4 use was based on self-reported information and used as a proxy for the diagnosis of hypothyroidism; in more than two thirds of these cases, we ascertained information from primary care physicians who provided validation in all but 1 case. Our analyses relating to clinical outcomes were restricted to hypothyroidism because there were few cases of hyperthyroidism. We found inconsistent associations in men, which likely reflects the lower prevalence of autoimmune thyroid disease in men and therefore reduced power, although there may be other explanations such as possible differences in pathogenesis between men and women.

Comparison with other studies

The prevalences of T_4 use, high anti-TPO antibodies, and previously undiagnosed overt or subclinical hypothyroidism were higher in women than in men, as expected, and were broadly similar to those reported in other population-based studies. In a large Danish survey, the prevalence of detectable anti-TPO antibodies (>30 U/mL) in women and men aged 60–65 years was 21.7% and 7.3%, respectively, and was higher in areas with moderate vs mild iodine deficiency (25). In a slightly older UK population (mean age 73 years) without known thyroid disease prior to biochemical screening, 4.1% of women and 2.4% of men had subclinical or overt hypothyroidism (21).

Among biochemically euthyroid study members with negative anti-TPO antibodies, we found no association between serum TSH concentration and BMI. Some, but not all, studies have reported positive associations between TSH concentrations and adiposity among euthyroid subjects (26). However, such associations may reflect adiposity driving a compensatory higher TSH secretion and hence higher thyroid hormone production, or higher serum TSH being a marker of relative thyroid hormone deficiency.

Previous smaller studies have suggested that thyroid function and thyroid disorders in women may have de-

velopmental origins. In a UK birth cohort study of 303 women (27), in those who had been bottle fed, serum free T_4 concentrations at age 60–71 years fell and serum TSH concentrations rose with increasing birth weight. In a Finnish birth cohort study of 293 women (28), those women ($n = 20$) with adult-onset hypothyroidism had lower birth weight and shorter birth length, and they remained shorter in early childhood and thinner during later childhood; at age 61 years, they were still shorter but had no differences in BMI than the other women, findings that are inconsistent with our larger study. Similarly, an initial observation of positive anti-TPO antibodies in lower-birth-weight twins was not confirmed in a larger cohort (29) or in our current analysis; however, the lack of data on gestational age is a further limitation of our study. In contrast, we found that weight gain after birth was positively associated with later T_4 use and positive thyroid autoantibodies in women.

Implications for the origins of thyroid autoimmunity

The mechanisms linking greater childhood weight gain and childhood overweight to hypothyroidism and thyroid autoimmunity in later life are unclear. They could include specific actions of adiposity or diet on thyroid hormone production or presentation of thyroid antigens to the immune system. Nutritional factors implicated in the risk of thyroid autoimmunity include iodine overload or supplementation and deficiencies of selenium, zinc, vitamin B12, and vitamin D (11), and these may be more prevalent in some overweight children. Alternatively, childhood weight gain and overweight may increase the risk of autoimmune disorders in general because similar positive associations with childhood weight status have been identified with the risk of other autoimmune diseases, such as type 1 diabetes (16, 30) and MS (17, 18). The potential effect sizes of childhood overweight or obesity on these outcomes are substantial, with approximately 2-fold higher relative risks for type 1 diabetes, MS, and thyroid autoimmunity. These autoimmune disorders share a number of genetic susceptibility loci involved in immune function (13), and obesity is associated with chronic low inflammation (31). Therefore, rapid childhood weight gain and adiposity could potentially trigger common pathogenic mechanisms to autoimmune disease, possibly by exacerbating specific inflammatory responses or by the actions of adipocytokines on reducing immune tolerance (15).

We did not have information on a family history of thyroid disease and autoimmunity to examine whether these associations might reflect a common genetic mechanism; however, there is yet no evidence of overlap be-

tween the genetic variants for autoimmune disease (13) and those for obesity (32). We suggest that future analyses could use genetic factors for obesity as instrumental variables to examine the causal relationship between weight gain and autoimmunity.

Conclusions

We identified novel associations between childhood weight gain, or childhood overweight, and later thyroid autoimmunity and hypothyroidism, particularly in women. These novel findings require confirmation in other studies, but they provide increasing support for the recommendation that finding mild thyroid dysfunction in overweight and obese individuals should not lead automatically to treatment but should prompt careful clinical and biochemical evaluation (1). Furthermore, we propose that a common mechanism links rapid childhood weight gain to the pathogenesis of autoimmune disorders in general, including thyroid autoimmunity. Although the prevention of childhood overweight is an established public health target, the identification of specific inflammatory or immune system pathways linking childhood adiposity to autoimmunity may allow potential future intervention in those at high risk of autoimmune disorders.

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SUPPLEMENTAL MATERIAL

JC-12-3761; "Childhood weight gain and thyroid autoimmunity at age 60-64 years: the 1946 British Birth Cohort study

Supplemental Table 1: Weight and BMI z-scores by thyroxine use in women at age 60-64 years.

	Use of Thyroxine		Yes <i>SE</i>	No <i>SE</i>	Yes <i>N</i>	No <i>N</i>	<i>P-value</i>
	Yes Mean	No Mean					
Weight at age (years):							
0	0.04	0.08	0.07	0.03	139	1133	0.6
2	-0.01	0.04	0.08	0.03	110	946	0.6
4	0.13	0.07	0.08	0.03	124	1015	0.6
6	0.20	0.05	0.08	0.03	126	950	0.1
7	0.18	0.05	0.08	0.03	127	940	0.2
11	0.33	0.04	0.08	0.03	122	938	0.002
14	0.30	0.03	0.08	0.03	118	865	0.003
20	0.26	0.02	0.07	0.03	118	947	0.01
26	0.19	0.01	0.07	0.03	122	997	0.04
36	0.21	-0.02	0.07	0.03	126	1039	0.01
43	0.15	-0.02	0.08	0.03	134	1066	0.07
53	0.21	-0.02	0.08	0.03	134	1063	0.01
60-64 years	0.20	-0.01	0.10	0.03	110	948	0.04
BMI at age (years):							
2	-0.04	0.00	0.09	0.03	102	870	0.7
4	0.04	0.00	0.08	0.03	116	970	0.7
6	0.05	0.01	0.08	0.03	120	905	0.7
7	0.11	-0.02	0.08	0.03	127	935	0.2
11	0.25	0.02	0.09	0.03	122	935	0.01
14	0.19	-0.01	0.08	0.03	116	856	0.02
20	0.22	0.01	0.08	0.03	115	940	0.03
26	0.14	-0.02	0.08	0.03	122	997	0.08
36	0.17	-0.05	0.08	0.03	124	1036	0.02
43	0.05	-0.04	0.09	0.03	132	1062	0.3
53	0.16	-0.03	0.08	0.03	134	1061	0.03
60-64 years	0.19	-0.02	0.10	0.03	110	947	0.04

Supplemental Table 2: Weight and BMI z-scores by anti-TPO antibody status in women at age 60-64 years.

	Anti-TPO				High N	Normal N	P-value
	High Mean	Normal Mean	High SE	Normal SE			
Weight at age (years):							
0	0.03	0.00	0.09	0.03	122	930	0.7
2	0.28	-0.04	0.11	0.03	107	767	0.002
4	0.19	-0.02	0.09	0.03	110	842	0.03
6	0.20	-0.03	0.09	0.03	103	788	0.02
7	0.17	-0.02	0.09	0.03	97	786	0.05
11	0.15	-0.02	0.10	0.03	103	782	0.09
14	0.25	-0.03	0.09	0.03	91	723	0.006
20	0.26	-0.03	0.09	0.03	100	789	0.005
26	0.15	-0.02	0.08	0.03	109	825	0.08
36	0.18	-0.02	0.09	0.03	116	854	0.03
43	0.15	-0.02	0.08	0.03	119	887	0.07
53	0.16	-0.02	0.09	0.03	120	894	0.05
60-64 years	0.17	-0.02	0.10	0.03	122	929	0.04
BMI at age (years):							
2	0.17	-0.02	0.10	0.04	95	709	0.1
4	0.13	-0.02	0.09	0.03	99	809	0.1
6	0.05	-0.01	0.09	0.03	94	755	0.3
7	0.13	-0.02	0.10	0.04	96	785	0.08
11	0.13	-0.02	0.11	0.03	103	779	0.07
14	0.23	-0.03	0.10	0.03	90	713	0.01
20	0.17	-0.02	0.10	0.04	100	783	0.07
26	0.11	-0.02	0.09	0.03	109	825	0.2
36	0.11	-0.02	0.09	0.03	115	853	0.2
43	0.08	-0.01	0.09	0.03	118	882	0.4
53	0.11	-0.01	0.09	0.03	120	893	0.1
60-64 years	0.15	-0.02	0.10	0.03	122	928	0.07

Anti-TPO antibody levels > 100 IU/ml were taken as indicative of thyroid autoimmunity