ISSN 2472-1972

Thyrotoxicosis in an Indigenous New Zealand Population – a Prospective Observational Study

Jade A.U. Tamatea,[1,2] Papaarangi Reid,[2] John V. Conaglen,[1] and Marianne S. Elston[1]

[1]Department of Medicine, Waikato Clinical Campus, University of Auckland. Private Bag 3200, Hamilton 3240, New Zealand; [2]Te Kupenga Hauora Māori, Tamaki Campus, University of Auckland. Private Bag 92019. Auckland 1142, New Zealand

ORCiD numbers: 0000-0002-4144-4316 (J. A.U. Tamatea); 0000-0003-2364-4776 (P. Reid); 0000-0003-0707-4988 (J. V. Conaglen); 0000-0002-0748-2300 (M. S. Elston).

ABSTRACT

Background: Reported international incidence rates of thyrotoxicosis vary markedly, ranging from 6 to 93 cases per 100 000 per annum. Along with population demographics, exposures, and study design factors, ethnicity is increasingly being recognized as a potential factor influencing incidence. This study aimed to document the epidemiology and clinical presentation of thyrotoxicosis for Māori, the indigenous population in New Zealand.

Methods: A prospective study of adult patients presenting with a first diagnosis of thyrotoxicosis between January 2013 and October 2014 to a single New Zealand center. Demographic data were collected, and detailed clinical assessment performed.

Results: With 375 patients, an incidence rate of thyrotoxicosis of 73.0 per 100 000 per annum was identified. Of these, 353 (94.1%) participated in the study. The median age of the cohort was 47 years, 81% were female, and 58% had Graves disease. The overall incidence of thyrotoxicosis for Māori, the indigenous people of New Zealand, was higher than non-Māori (123.9 vs 57.3 per 100 000 per annum). Rates of both Graves disease and toxic multinodular goiter were higher in Māori as compared to non-Māori (incidence rate ratios of 1.9 [1.4, 2.6] and 5.3 [3.4, 8.3], respectively), with this increase being maintained after controlling for age, deprivation, and smoking.

Conclusions: Māori, the indigenous people of New Zealand, have an increased incidence of thyrotoxicosis compared to non-Māori and, in particular, toxic multinodular goiter. A greater understanding of the epidemiology of thyrotoxicosis in other indigenous and marginalized ethnic groups may help to optimize therapeutic pathways, equitable care and outcomes.

Key Words: thyrotoxicosis, hyperthyroidism, ethnicity, indigenous, inequity/disparity, incidence

Thyrotoxicosis is a common endocrine condition with published incidence rates varying markedly in differing populations, from 6 to 93 cases per 100 000 per annum (p100 000pa)

Abbreviations: CI, confidence interval; FT3, free triiodothyronine; FT4, free thyroxine; GD, Graves disease; IR, incidence rate; IRR, incidence rate ratio; p100,000pa, per 100 000 per annum; STA, solitary toxic adenoma; TMNG, toxic multinodular goiter; TSH, thyroid-stimulating hormone; WHO, World Health Organization.

Received 22 October 2019
Accepted 28 January 2020
First Published Online 29 January 2020
Corrected and Typeset 7 March 2020.

[1]. In addition to population differences (including age distribution, iodine exposure, and genetic influences), varying study methods (eg, case identification and inclusion/exclusion criteria used) may also influence incidence rates. As a result, comparing thyrotoxicosis incidence rates across studies can be difficult.

Ethnic variations in the incidence of thyrotoxicosis have been described in other populations. Rates of Graves disease (GD) are reported to be higher in American Black and Pacific Island/Asian ethnic groups [2], and all-cause thyrotoxicosis higher in American Black individuals [3] when compared with their non-Hispanic White counterparts. A 2012 Endocrine Society scientific statement focused on health disparities reported on ethnic differences in the prevalence of hyperthyroidism, thyroid antibody, and urinary iodine concentrations in American population studies. This group recommended additional studies to quantify and understand these variances [4]. However, limited information is available outside of North America. Equally, there are limited data published on ethnic differences for other specific causes of thyrotoxicosis, for example, toxic multinodular goiter (TMNG). There have been no reports of differences in severity of thyrotoxicosis across ethnic groups; however, factors such as age, stress, and smoking history have been associated with differing clinical severity of thyrotoxicosis.

Previous incidence rates of thyrotoxicosis in New Zealand have varied widely. In 1928, Jones reported an incidence of "toxic goitre [sic]" in hospital inpatients of 88 per one-thousand admissions, much higher than that of Australia at that time [5]. The only other New Zealand incidence study, performed prior to the availability of highly sensitive thyroid-stimulating hormone (TSH) testing, reported an annual incidence rate of 25.8 p100 000pa [6].

As is the experience of many indigenous populations, Māori, the Tangata Whenua (indigenous people) of New Zealand, experience poorer health outcomes across a wide spectrum of conditions [7]. However, the incidence of thyrotoxicosis in Māori is unknown, as previous epidemiological studies of thyrotoxicosis have not included a representative cohort of Māori participants [5, 6]. In 2 retrospective New Zealand thyrotoxicosis definitive therapy studies, the proportion of the Māori was higher than expected for the source population, particularly for patients with TMNG; however, due to the retrospective nature of the studies, an increased prevalence simply due to referral bias and/or delays was unable to be excluded [8].

This study aimed to investigate the epidemiology of thyrotoxicosis for this indigenous group and compare that with the non-indigenous population.

1. Materials and Methods

A. Methodology

The objective of this study was to describe the epidemiology and clinical presentation of thyrotoxicosis in the New Zealand indigenous population, based on a hypothesis that Māori have a higher incidence and increased severity of thyrotoxicosis than non-Māori due to a combination of personal, social, and systemic factors. This research is framed within a kaupapa Māori epidemiology methodology [9], where Māori are positioned at the center, recognizing the impact a colonial history has on current health inequalities for an indigenous population (eg, social deprivation and reduced access to care).

B. Data Collection

Ethical approval for this study was obtained from the New Zealand Northern B Health and Disability ethics committee (13/NTB/4) and was prospectively registered on the Australian New Zealand Clinical Trials Registry (ACTRN: 12613000210774). Written, informed consent was obtained from all participants in accordance with the principles set out in the Declaration of Helsinki, with additional considerations to align to a kaupapa Māori methodology.

The Waikato District Health Board area covers a population of 281 724 adults, of whom 17.3% are Māori (compared to 11.8% in the national 3 376 416 population). Given the predominance of public (socialized) medicine in New Zealand, the local public hospital cares for all living within the region, with very low care delivered outside of the area. As 5% of New Zealand health care costs reside in the private health care service [10], patients from both of the 2 private endocrinologists were also included in the study. The usual practice in our region is for the referral of all patients diagnosed with endogenous thyrotoxicosis to a specialist endocrine service. All patients (>15 years of age) with a first diagnosis of thyrotoxicosis (TSH <0.1mIU/L) between January 2013 and October 2014 were invited to participate. Patients with iatrogenic hyperthyroidism, hyperthyroidism in pregnancy, transient hyperthyroidism (only 1 TSH recording <0.1mIU/L), and those residing outside of the catchment area or unable to give informed consent were excluded.

Clinical and demographic data were collected on all patients at their first specialist appointment. In New Zealand, ethnicity is classified by self-identity. It does not attempt to measure ancestry or a blood quantum, although all who identify as Māori would be expected to have Māori ancestry. Ethnicity is a common variable for describing differences in population groups, and in this study, ethnicity information was collected using the same method as with the New Zealand national census for consistency [11]. Results were presented as categorical "Māori" and "non-Māori" variables, using a prioritization process to manage multiple ethnicities [12]. Social deprivation was measured using the New Zealand Deprivation Index 2013 [13], a decile scale of social deprivation for populations, (a value of 10 being the most deprived 10% of small areas in New Zealand) and the New Zealand Index of Socioeconomic Deprivation for Individuals, a questionnaire of 8 questions of markers of deprivation [14]. Population data, with relevant demographics, were derived from the New Zealand 2013 census.

Clinical, laboratory, and radiology findings were used to ascertain the cause of thyrotoxicosis (Graves disease, TMNG, solitary toxic adenoma [STA], thyroiditis, amiodarone-induced thyrotoxicosis, and iodine-induced hyperthyroidism based on natural history, recent exposure history, findings on ultrasound and ^{99m}technetium isotope scan, TSH receptor antibody positivity [≥4.0 IU/L]). Severity of thyrotoxicosis was determined by both clinical and biochemical measures. Clinical severity was determined using Wayne's index, a diagnostic scoring system of thyrotoxicosis severity using symptoms and signs [15]. The highest available serum free thyroxine (FT_4) and free triiodothyronine (FT_3; [peak FT_4 and peak FT_3]) was used to determine biochemical severity of thyrotoxicosis in univariate analysis, with FT_3 the preferred outcome for multivariate analysis. Both serum FT_4 and FT_3 were measured on a Roche Modular Analytics E170 immunoassay (Roche Diagnostics, Mannheim, Germany) at the hospital-based laboratory or using a Beckman-Coulter Access immunoassay at the community-based laboratory, with results normalized between assays for comparison. Thyroid volume was calculated on ultrasound using an ellipsoid formula of depth, width, and length of each lobe of the thyroid with a correction factor of 0.479, as recommended by the World Health Organization (WHO) [16]. Peak systolic velocity was measured using color Doppler of the right inferior thyroid artery [17].

C. Statistical Analysis

All analyses were carried out using STATA 13 (StataCorp. 2013, Stata Statistical Software: Release 13. College Station, TX: StataCorp LP) or the *Analytical Tools for Public Health* [18].

Continuous variables are expressed as mean or geometric mean (95% confidence intervals [CIs]) following logarithmic transformation, according to their distribution. Student *t*-test analyses were used to compare means. Categorical variables are expressed as a number (percentage) with Chi Square or Fisher exact analyses done, according to count. Ordinal variables are expressed as median (range) with Mann-Whitney analyses to compare medians. Incidence rates (IR) were calculated using the number of cases divided by the adult population, according to the New Zealand census 2013, with that result adjusted for

p100 000pa. Incidence rate ratios (IRR) were calculated by comparing 2 IR to each other. Results for both IR and IRR are presented with 95% CIs. All comparisons are include Māori compared with non-Māori, other than base IRs in which Māori compared with Europeans are included for sensitivity analysis.

Standardized IRs were calculated by direct standardization, using the national Māori population as the standard, in keeping with the kaupapa Māori methodology that underpinned this study [9]. This indigenous population standard was used because international population standards, such as the WHO [19] or Segi [20], have been shown to misrepresent the generally younger Māori population [21]. For international comparison, direct age-standardization using Segi and WHO standard populations was also undertaken.

Negative binomial regression was used because of overdispersion to control for confounders of incidence (presented as IRR) and linear regression for log [10]-transformed severity outcomes (with coefficients back-transformed and presented as percentage difference).

A P value of <0.05, or IRR CIs that do not cross 1.00 were used to reject the null hypothesis.

2. RESULTS

Within the study period, 375 individuals met the inclusion criteria, of which 353 (94.1%) participants consented to participate (19 participants excluded, 4 Māori). A recruitment flow diagram is shown in Figure 1.

Based on the 375 eligible referrals received, the IR of thyrotoxicosis in Waikato, New Zealand, is 73.0 p100,000pa (95% CI, 65.8–80.8). Data from the 353 participants (median age 47 years, 81% female, 58% GD, 8% subclinical disease [predominantly TMNG diagnosis, 66.7%]) were used for all other analyses. Table 1 describes the cohort in this study, and Table 2 presents thyrotoxicosis annual IRs.

A. Incidence by Ethnicity

A total of 109 participants were of Māori ethnicity, leaving 244 who were non-Māori (European 87.3%, Asian 8.6%, Pacific Peoples 3.3%, and Middle Eastern/Latin American/African 0.8%). Māori were a median of 6 years younger and were more likely to reside in an area with the most material deprivation ($P < 0.0005$). Māori were also more likely to have ever smoked ($P = 0.003$) and had lower rates of private health care utilization ($P = 0.006$) (Table 1). The only clinical baseline difference noted was a higher body mass index at presentation in Māori when compared with non-Māori. This was despite an increased percentage weight loss reported for Māori participants compared with non-Māori participants (12.1% vs 8.7% loss of premorbid bodyweight, $P < 0.0005$).

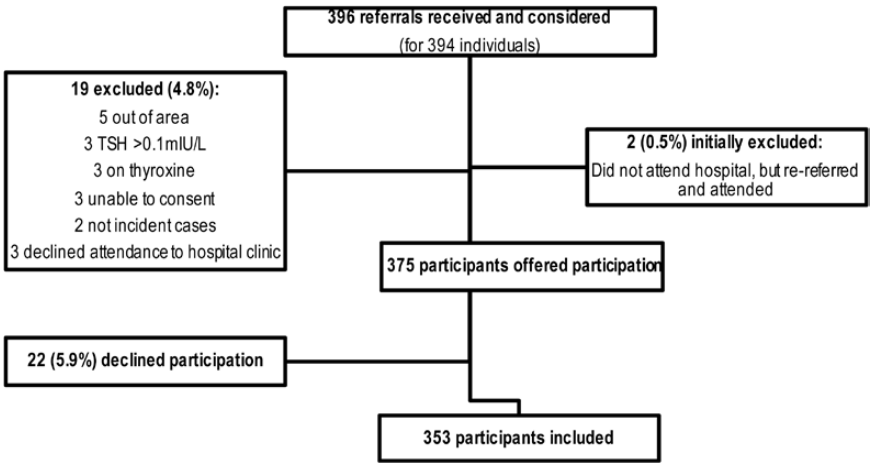

Figure 1. Flow diagram of participants included in the observational study. TSH, thyroid-stimulating hormone.

Table 1. BaselineCharacteristics

		Māori n=109 (n[a] 58)		Non-Māori n=244 (n[a] 145)		*P*
Age	Median age	44	22, 71	50	22,77	0.008
	15–39 years	46	42.2%	72	29.5%	0.062
	40–64 years	46	42.2%	122	50.0%	
	65 years and older	17	15.6%	50	20.5%	
Gender	Female	92	84.4%	194	79.5%	0.279
	Male	17	15.6%	50	20.5%	
Diagnosis	Graves disease	58	53.2%	145	59.4%	<0.0005
	TMNG	33	30.3%	30	12.3%	
	Other	18	16.5%	69	28.3%	
Social deprivation	Median NZDep2013	9	2, 10	6	1, 10	<0.0005
	Least deprivation	10	9.2%	90	24.6%	<0.0005
	Moderate deprivation	32	29.3%	105	43.0%	
	Most deprivation	67	61.5%	79	32.4%	
	Private health care	3	2.8%	29	11.9%	0.006
Smoking history	Ever smoked	75	68.8%	127	52.1%	0.003
	Never smoked	34	31.2%	117	47.9%	
Clinical	Mean body mass index (kg/m^2)	27.8	26.6, 29.1	26.3	25.6, 27.1	0.032
	History of autoimmune disease[a]	5	8.6%	9	6.2%	0.540
	Family history of thyroid disease	42	38.5%	111	45.5%	0.223
	Family history of autoimmune disease[a]	18	31.0%	63	43.5%	0.103

Continuous variables expressed as median with 5th/95th percentiles or mean with 95% CIs. Categorical variables expressed as number with percentage and ordinal variables expressed as median with range. Least deprivation: resides in an area with NZDep decile 1–3. Median deprivation: resides in an area with NZDep decile 4–7. Most deprivation: resides in an area with NZDep decile 8–10.Abbreviations: NZDep2013, New Zealand index of deprivation 2013 [13]; TMNG, toxic multinodular goiter.
[a] Graves disease participants only.

Māori had a higher annual crude IR of thyrotoxicosis than non-Māori (123.9 vs 57.3 p100,000pa; IRR 2.2 [1.7–2.7]), which was increased across all ages (Figure 2) and across the 2 most common diagnoses, GD (IRR 1.9 [1.4–2.6]) and TMNG (IRR 5.3 [3.4–8.3]) (Table 3). Non-Māori had higher amounts of amiodarone-induced thyrotoxicosis and STA (Tables 2 and 3), but small numbers make it hard to make determinations of accuracy. These results were unchanged when Māori were compared with Europeans only (Table 3). Elevated IRRs for Māori were maintained after stratifying for confounding factors (eg, age, deprivation, and smoking behavior; Table 4) or standardizing for age and social deprivation (IRR 2.3 [1.8–2.8]) (Table 5).

Negative binomial regression modeling, controlling for age, diagnosis, smoking history, and social deprivation identified interactions between ethnicity and diagnosis ($P = 0.0002$). To manage this, the model investigating the effect of ethnicity on thyrotoxicosis incidence was stratified by diagnosis. This analysis showed that the IRR between Māori and non-Māori was changed after controlling for smoking (GD IRR reduced to 1.6 [1.2–2.3]; TMNG IRR increased to 6.3 [3.7–10.9]), but in both cases remained elevated. Having never smoked was associated with a lower IR of thyrotoxicosis (IRR 0.6 [0.4–0.8] as compared with a current smoker) (Table 6).

B. Clinical Presentation by Ethnicity

Clinically, there was little difference in presentation between 2 two groups (Table 7). While overall admission rates were not different between Māori and non-Māori, there was an increase in hospitalization for thyrotoxic periodic paralysis in Māori. Simple univariate comparison of clinical severity (Wayne's index score) and biochemical severity (peak FT_3) demonstrated no difference between Māori and non-Māori. However, univariate linear regression, stratified

Table 2. Annual Incidence Rate of Thyrotoxicosis

	n (n Māori)	Incidence Rate Total (95% CI)	Incidence Rate Ratio (95% CI)
Gender			
Female	286	107.2 (95.5, 120.4)	4.0 (3.1, 5.1)
Male	67	27.2 (21.4, 34.5)	
Age			
15–39 years	118	56.8 (47.4, 68.0)	1.00
40–65 years	168	79.8 (68.2, 93.8)	1.4 (1.1, 1.8)[a]
65 years and older	67	69.1 (53.5, 87.7)	1.2 (0.9, 1.7)[a]
Ethnicity			
Māori	109	123.9 (102.7, 149.5)	2.2 (1.7, 2.7)
Non-Māori	244	57.3 (50.6, 65.0)	
Diagnosis			
Graves disease	203 (58)	39.5 (34.5, 45.4)	
TMNG	63 (33)	12.3 (9.6, 15.7)	
Thyroiditis	50 (12)	9.7 (7.4, 12.9)	
Amiodarone-induced thyrotoxicosis	13 (2)	2.5 (1.5, 4.4)	
Solitary toxic adenoma	12 (1)	2.3 (1.3, 4.1)	
Iodine-associated hyperthyroidism	9 (2)	1.8 (0.9, 3.4)	
Social deprivation (NZDep2013)			
Least deprivation	70	78.6 (62.2, 99.3)	1.0
Moderate deprivation	137	72.7 (61.5, 86.0)	0.9 (0.7, 1.3)[a]
Most deprivation	146	61.9 (52.6, 71.7)	0.8 (0.6, 1.1)[a]
Smoking behavior			
Ever smoked	202	106.5 (92.8, 122.3)	2.0 (1.6, 2.4)
Never smoked	151	54.2 (46.24, 63.61)	

Presented as incidence rates (per 100 000 per year) and incidence rate ratio with 95% CIs. An incidence rate ratio with 95% CIs not crossing 1.00 is considered significant.
Abbreviations: CI, confidence interval; NZDep2013, New Zealand index of deprivation 2013 [13]; TMNG, toxic multinodular goiter. Least deprivation: resides in an area with NZDep decile 1–3. Median deprivation: resides in an area with NZDep decile 4–7. Most deprivation: resides in an area with NZDep decile 8–10.
[a] Incidence rate ratio compared with first group (youngest age, least deprivation).

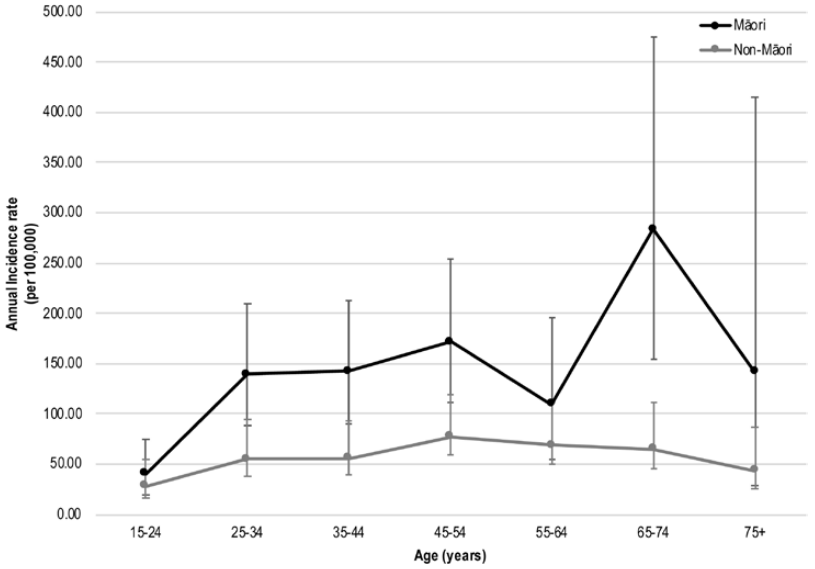

Figure 2. Annual incidence rates of all-cause thyrotoxicosis over 10-year age bands, Māori vs non-Māori.

by age due to an identified interaction, found some evidence of a higher Wayne's index (34% increase, $P = 0.13$) and peak FT_3 (35% increase, $P = 0.012$) in young Māori (15–39 years), but lower peak FT_3 (22% reduction, $P = 0.011$) in Māori aged 40 to 64, when compared with

Table 3 Incidence Rate Ratio of All-Cause Thyrotoxicosis; Māori Vs Non-Māori and Māori vs European

	IRR (95% CI)	
	Māori vs non-Māori	**Māori vs European**
Crude annual incidence rates		
All-cause thyrotoxicosis	2.2 (1.7, 2.7)	2.0 (1.6, 2.5)
GD	1.9 (1.4, 2.6)	1.9 (1.4, 2.5)
TMNG	5.3 (3.4, 8.3)	4.6 (2.9, 7.2)
Other	1.3 (0.8, 2.1)	1.1 (0.7, 1.8)

Presented as IRR (95% CI). An IRR with 95% CIs not crossing 1.00 considered significant.
Presented as IRR (95% CI). An IRR with 95% CIs not crossing 1.00 considered significant.CI, confidence interval; GD, Graves disease; IRR, incidence rate ratio, TMNG, toxic multinodular goiter.

Table 4. Comparison of Māori and Non-Māori Incidence Rates of All-Cause Thyrotoxicosis, Stratified by Confounding Variables

		Incidence Rate (95% CI)			
	n	**Māori**	**n**	**Non-Māori**	**Incidence Rate Ratio (95% CI)**
Age					
15–39 years	46	94.6 (70.9, 126.3)	72	45.3 (36.0, 57.1)	2.09 (1.45, 2.99)
40–64 years	46	141.4 (105.9, 188.8)	122	68.6 (57.5, 81.9)	2.06 (1.48, 2.87)
65 and older	17	249.9 (155.4, 400.0)	50	56.2 (42.6, 74.2)	4.45 (2.69, 7.35)
Gender					
Female	92	195.6 (159.4, 239.9)	194	88.3 (76.7, 101.6)	2.22 (1.74, 2.82)
Male	17	41.6 (25.8, 66.9)	50	24.3 (18.4, 32.1)	1.71 (0.99, 2.95)
Subclinical disease					
Clinical disease	98	110.0 (89.3, 134.1)	228	53.5 (46.8, 60.9)	2.06 (1.61, 2.62)
Subclinical disease	11	12.4 (6.2, 22.1)	16	3.8 (2.1, 6.1)	3.29 (1.38, 7.55)
Social deprivation					
Least deprivation	10	74.0 (39.8, 137.5)	60	79.4 (61.6, 102.3)	0.93 (0.48, 1.82)
Medium deprivation	32	102.4 (72.4, 144.9)	105	66.8 (55.2, 80.9)	1.53 (1.03, 2.27)
Most deprivation	67	155.1 (122.1, 197.1)	79	41.0 (32.9, 51.1)	3.79 (2.80, 5.13)
Smoking behavior					
Never smoked	34	93.5 (66.8, 130.9)	117	48.3 (40.3, 57.9)	1.93 (1.33, 2.82)
Ever smoked	75	158.4 (126.3, 198.6)	127	89.3 (75.0, 106.2)	1.77 (1.24, 2.35)

Presented as incidence rates (per 100 000 per year) and incidence rate ratio with 95% CIs. An incidence rate ratio with 95% CIs not crossing 1.00 is considered significant. Least deprivation: resides in an area with NZDep decile 1–3. Median deprivation: resides in an area with NZDep decile 4–7. Most deprivation: resides in an area with NZDep decile 8–10.
Abbreviation: NZDep2013, New Zealand index of deprivation 2013.[13]

non-Māori of the same age group. Māori participants had 53% larger thyroid glands on ultrasound. After multivariate linear regression analyses, controlling for age, gender, diagnosis, social deprivation, private health care, smoking history, and treatment delay in all analyses and, in addition, body mass index in thyroid volume analysis, there was no difference in Wayne's index ($P = 0.170$), and a reduction seen in the difference of peak FT_3 (29% increase, $P = 0.039$), and a reduction in difference of thyroid volume (28% increase, $P = 0.003$).

3. Discussion

This prospective study demonstrates an overall incidence of thyrotoxicosis in New Zealand of 73.0 p100,000pa within a region of the world that has not previously been well represented. This incidence is higher than most comparable international [1] or New Zealand studies

Table 5. Age-Standardized Incidence Rates of Thyrotoxicosis Based on Different Age Population Standards; Māori Vs Non-Māori

Standard Population		Crude Incidence		New Zealand Māori Population		Segi Population		WHO Population	
		IR (95%CI)	IRR (95%CI)	IR (95%CI)	IRR (95%CI)	IR (95%CI)	IRR (95%CI)	IR (95%CI)	IRR (95%CI)
All-cause thyrotoxicosis	Māori	123.9 (101.8, 149.5)	2.16 (1.71, 2.72)	124.9 (101.4, 148.3)	2.27 (1.81, 2.84)	127.3 (103.4, 151.2)	2.32 (1.85, 2.91)	128.6 (104.4, 152.7)	2.34 (1.87, 2.94)
	Non-Māori	57.3 (50.4, 65.0)		55.0 (48.1, 61.9)		54.9 (48.0, 61.8)		54.8 (47.9, 61.7)	
	Total population	68.7 (61.8, 76.3)		66.6 (59.7, 73.6)		66.5 (60.0, 73.5)		66.5 (59.6, 73.5)	
Graves disease	Māori	69 (50.1, 85.3)	1.94 (1.44, 2.61)	65.8 (48.8, 82.7)	1.92 (1.41, 2.60)	65.4 (48.5, 82.2)	1.92 (1.42, 2.61)	65.1 (48.4, 81.9)	1.93 (1.42, 2.61)
	Non-Māori	34.1 (28.8, 40.1)		34.3 (28.7, 39.9)		34 (28.4, 39.5)		33.8 (28.3, 39.3)	
	Total population	39.5 (34.5, 45.4)		40.9 (35.2, 46.5)		40.4 (34.9, 46.0)		40.3 (34.7, 45.8)	
Toxic multinodular goiter	Māori	37.2 (25.8, 52.7)	5.32 (3.42, 8.27)	38.6 (25.4, 51.8)	7.46 (4.55, 12.22)	41.3 (27.2, 55.3)	7.78 (4.75, 12.76)	42.6 (28.0, 57.2)	7.93 (4.84, 13.00)
	Non-Māori	7.1 (4.8, 10.1)		5.2 (3.3, 7.0)		5.3 (3.4, 7.2)		5.4 (3.5, 7.3)	
	Total population	12.3 (9.6, 15.7)		9.4 (7.1, 11.7)		9.6 (7.2, 12.0)		9.7 (7.3, 12.1)	

Presented as IR (95% CI) or IRR (95% CI). IRR 95% CIs not crossing 1.00 is considered significant.
Abbreviations: CI, confidence interval; GD, Graves disease; IR, incidence rate (per 100 000 persons per year); IRR, incidence rate ratio; TMNG, toxic multinodular goiter.

Table 6. Negative Binomial Regression for Factors Influencing Thyrotoxicosis Incidence

			Incidence Rate Ratio (95% CI)
Ethnicity (Māori vs non-Māori)	**Diagnosis**	Graves disease	1.6 (1.2, 2.3)
		TMNG	6.3 (3.7, 10.9)
		Other	1.2 (0.7, 2.0)
Age	15–39 years		1.0
	40–64 years		1.4 (1.1, 1.9)
	65+ years		1.5 (1.0, 2.2)
Social deprivation (NZDep2013)	Least deprivation		1.0
	Median deprivation		0.9 (0.6, 1.3)
	Most deprivation		1.0 (0.7, 1.4)
Smoking history	Current smoker		1.0
	Ex-smoker		1.1 (0.8, 1.6)
	Never smoked		0.6 (0.4, 0.8)

Model includes ethnicity, age, diagnosis, deprivation and smoking. Ethnicity stratified by diagnosis due to interactions. Presented as incidence rates (per 100 000 per year) and incidence rate ratio with 95% CIs. An incidence rate ratio with 95% CIs not crossing 1.00 is considered significant.
Abbreviations: CI, confidence interval; NZDep2013, New Zealand index of deprivation 2013 [13]; TMNG, toxic multinodular goiter. Least deprivation: resides in an area with NZDep decile 1–3. Median deprivation: resides in an area with NZDep decile 4–7. Most deprivation: resides in an area with NZDep decile 8–10.

Table 7. Clinical Presentation With All-Cause Thyrotoxicosis, by Ethnicity

		Māori n=109 (n[b] 58)		**Non-Māori n=244 (n[b] 145)**		***P***
Admissions	Hospital admission	19	17.4%	27	11.1%	0.101
	For thyrotoxicosis	12	11.0%	15	6.2%	0.112
	For cardiac complication	6	5.5%	15	6.2%	0.813
	For periodic paralysis	4	3.7%	0	0.0%	0.003
	For psychiatric complication	2	1.8%	2	0.8%	0.405
Clinical findings	Mean Wayne's index score	14.5	12.5, 16.6	12.1	10.8, 13.5	0.053
	Mean[a] percentage weight loss (%)	12.1	10.4, 14.0	8.7	8.0, 9.6	<0.0005
	Mean heart rate	86	82, 90	86	83, 88	0.980
	Irregular heart rate	7	6.4%	18	7.4%	0.747
	Presence of heart failure	8	7.3%	15	6.2%	0.675
Laboratory results	Mean[a] peak FT_4 level (pmol/L) [RR 7–16]	27.6	24.7, 30.9	29.3	27.5, 31.2	0.337
	Mean[a] peak FT_3 level (pmol/L) [RR 3.6–6.5]	11.1	9.8, 12.6	11	10.3, 11.8	0.932
	Mean[a] TRAb[b] (mIU/L) [RR < 1.3mIU/L]	9.3	7.3, 11.8	7.8	6.8, 9.1	0.240
Radiology	Mean[a] ultrasound volume (mL)					
	Graves disease	26.5	22.6, 31.2	19	17.0, 21.0	<0.0005
	TMNG	34.4	25.7, 46.0	29.9	22.9, 38.9	0.466
	Mean[a] peak systolic velocity (cm/sec)[b]	67.5	55.8, 81.6	70.2	64.0, 77.0	0.676

Continuous variables expressed as median with 5th/95th percentiles or mean with 95% CIs. Categorical variables expressed as number with percentage, and ordinal variables expressed as median with range.
Abbreviations: CI, confidence interval; FT_3, free triiodothyronine; FT_4, free thyroxine; RR, reference range; TMNG, toxic multinodular goiter; TRAb, thyroid-stimulating hormone receptor antibody
[a] Geometric mean. [b] Graves disease participants only.

[5, 6]. This higher incidence in New Zealand may be contributed to by more comprehensive identification of cases (public and private health care; sensitive TSH assays compared with an older study) or an increase in the rate of thyrotoxicosis in New Zealand since previous reports.

This study is the first to investigate the incidence of thyrotoxicosis in Māori, the New Zealand indigenous population. The overall incidence of thyrotoxicosis in Māori (123.9 p100,000pa) was more than double that of non-Māori population. While Māori demonstrated an increased incidence of GD (IRR 1.9), the most marked difference was for TMNG (IRR 5.3). When age, smoking, and deprivation were controlled for, GD rate was 1.6 times higher and TMNG was 6.3 times higher in Māori. Correspondingly, there was less amiodarone-induced thyrotoxicosis and STA in Māori, although information on prevalence of amiodarone prescribing in these communities is not known.

While ethnic differences in TMNG incidence is new, incidence differences in GD or all-cause thyrotoxicosis have been shown previously. McLeod et al reported GD higher incidence rates in American military personnel in Black and Pacific Island/Asian populations compared with non-Hispanic White counterparts [2]. Similarly, in American military personnel, an incidence of all-cause thyrotoxicosis in Black female soldiers was 1.7 times higher than the non-Hispanic white incidence that has been reported [3].

Outside of America, within a South African population, incidence of all-cause thyrotoxicosis in black women (23 p100,000pa) was less than half the rate of the comparison group [22]. However, the incidence was increasing rapidly within this group, thought to be due to increasing recognition of the diagnosis, calling into question the difference in incidence seen in this hospital-based study from the 1970's apartheid-era Johannesburg. The influence of thyrotoxicosis recognition is an important consideration when measuring incidence in marginalized populations. In our hospital-based incidence study, underdiagnosis or under-referral due to disparities in health care access and treatment experienced by Māori may influence results [7]. However, underdiagnosis in Māori will have led to an underestimate in the difference of thyrotoxicosis incidence between these 2 populations.

Neither clinical ($P = 0.053$) nor biochemical ($P = 0.932$) severity were different when the total Māori cohort were compared to non-Māori. Within patients aged 15 to 39 years, Māori had a 34% increase in Wayne's index and 35% increase in FT_3 levels. This difference was not seen, or reduced in magnitude, after controlling for contributing factors. This inverse relationship between severity and age is well established [23].

Māori thyrotoxic patients had larger thyroid glands when compared with non-Māori patients, even after controlling for available confounding variables, including diagnosis. Thyroid volume may influence compressive symptoms or be associated with a reduced response to radioactive iodine and antithyroid drug therapy [24]. Differences in thyroid size have been documented between ethnic groups. Kalk et al reported from South Africa a 12.8 g increase in thyroid size for thyrotoxic Black patients compared with thyrotoxic White patients [25]. In nontoxic populations, increased rates of large thyroid glands have been noted in American Black populations [26] as well as in Brazilian Black and 'Mullato' children [27] when compared with local white comparison cohorts. In individuals without thyroid disease, multiple factors are reported to influence thyroid volume, including genetics, gender, and biometrics as well as environmental exposures including iodine, alcohol, and cigarette smoke [28]. However, the factors driving an ethnic difference in thyroid volume are not known and it is unclear if there is an ethnic difference in thyroid size in euthyroid Māori and non-Māori in the community.

Ethnic differences in thyrotoxicosis rates and clinical presentation have been theorized to be due to dietary variations (particularly iodine) [2], migratory/urbanization [22], negative life experiences [2, 22], and age [23]. Māori in this study, similar to the euthyroid population, had increased social deprivation. Increasing social deprivation increased the difference in thyrotoxicosis incidence between Māori and non-Māori (Table 4) while not effecting incidence in the overall population. This is similar to a United Kingdom study

demonstrating incremental IR increases of subclinical thyrotoxicosis for each quintile of deprivation [29]. Others have failed to show an impact of deprivation [30]. African American and Pacific Island/Asian populations in America, share a history of marginalization with Māori in New Zealand, living within a power imbalance. Smith et al suggests living with the increased negative life events related to racism, overt and systemic, is related to poor health [31]. While the effect of acute stress has been postulated to influence GD presentation [32], the effect of racism and/or negative life events has not been investigated. The role, if any, in TMNG is not known.

Smoking has been linked with increased rates of GD (but not TMNG) [33] and increased clinical severity of thyrotoxicosis at presentation [23]. A history of tobacco use, which was more common in the Māori cohort, was associated with twice the incidence of thyrotoxicosis compared with lifetime nonsmokers and reduced the IRR between Māori and non-Māori with GD. Unlike previous studies, smoking did not appear to influence clinical or biochemical severity of thyrotoxicosis nor thyroid volume.

Aligned to the kaupapa Māori foundation of this study, it is recognized that inequities in the distribution of and access to the determinants of health are the real-life postcolonial experience of Māori [34]. These determinants were considered as confounders in this study, but it is acknowledged that these may help understand the drivers of disparity but do not eliminate the difference. The absolute variances between Māori and non-Māori are the reality of thyrotoxicosis for our community and need clear documenting for resource allocation.

This is the largest incidence and clinical study of thyrotoxicosis in New Zealand, is the first within the indigenous population, and offers recent data from a region previously poorly covered. However, there are limitations. The study was based in 1 locale and may have been strengthened by a national cohort. While many confounders were considered, residual confounders might exist to explain the differences seen. Additionally, as a hospital-based incidence study, it is subject to referral biases. Public and private endocrine specialists were included, making it unlikely to have missed individuals in the area. Participation rates in the study were very high (94.1%), with ethnic parity in participation. This observational cohort gives a snapshot of approximately 2 years and cannot clarify if this is a transient ethnic difference, but it is supported by increased thyrotoxicosis prevalence in previous Māori cohorts in the region [8, 35]. Likewise, information regarding daily stress, including self-reported experiences of racism, were not collected and could have been useful in further understanding the differences seen between Māori and non-Māori. We have no data on iodine or other micronutrient intake for the participants in this study. Since records began, New Zealand has been known to be iodine deficient due to low soil iodine [36]. This resulted in the introduction of iodination of salt in 1924, although levels were not adequately fortified until 1938 [37]. Due to a decline in iodine levels in the 1990s, fortification of bread (with iodized salt) began in 2009 [38] and supplementation in pregnancy in 2010 [39]. While recent iodine intake information in New Zealand suggests the population has become iodine replete [40], ethnic differences have not been studied. Additionally, current iodine intake may not be indicative of past consumption, and adequate iodine now would not preclude a history of deficiency. There are no data on differences in iodine intake between Māori and non-Māori, both absolute (total current iodine intake) and relative (historical iodine intake changes since colonization or in personal intake changes since childhood).

4. CONCLUSION

This prospective study of thyrotoxicosis demonstrates an increased incidence of thyrotoxicosis for Māori in New Zealand of more than double the rate measured in non-Māori population. Of particular note, an over 6-fold increase in TMNG was identified in Māori with thyrotoxicosis. Increased markers of severity, clinical, and biochemical in young Māori and thyroid volume in all were also noted. In order to improve health outcomes for Māori, it is

important to further understand these ethnic disparities; understanding disease pathogenesis, developing diagnostic pathways, and ensuring the appropriate allocation of funding will ensure equitable care and outcomes.

ACKNOWLEDGEMENTS

The authors wish to acknowledge Dr Joanna Stewart for her assistance and guidance with statistical analyses and Ms Carol Jarvis for her support with data entry and participant coordination.

***Financial Support*:** The Health Research Council and Royal Australasian College of Physicians are acknowledged for their financial support of Dr Jade Tamatea and this project. M. E. received, and J. V. C. and J. T. were named on, an emerging researcher project grant from the Health Research Council of New Zealand (13/770). J. T. received PhD scholarships from the Health Research Council of New Zealand (14/074) and the Royal Australasian College of Physicians.

***Clinical Trial Information*:** Australian New Zealand Clinical Trials Registry TRIAL ID: ACTRN12613000210774 (21 February 2013).

Author Contributions: Literature search, data collection, data analysis, and draft manuscript writing was undertaken by J.T. Study design, data collection, and interpretation and contribution to development of the final manuscript was undertaken by all authors.

Additional Information

Correspondence: Jade Tamatea, Peter Rothwell Academic Centre, Waikato Clinical Campus, University of Auckland. Private Bag 3200, Hamilton 3240, New Zealand. E-mail: jade.tamatea@waikatodhb.health.nz.

Disclosure Summary: The funding source played no role in study design; collection, analysis, or interpretation of data; writing the report; or the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

References

1. Taylor PN, Albrecht D, Scholz A, et al. Global epidemiology of hyperthyroidism and hypothyroidism. *Nat Rev Endocrinol*. 2018;**14**(5):301–316.
2. McLeod DS, Caturegli P, Cooper DS, Matos PG, Hutfless S. Variation in rates of autoimmune thyroid disease by race/ethnicity in US military personnel. *JAMA*. 2014;**311**(15):1563–1565.
3. Thyroid disorders among active component military members, U.S. Armed Forces, 2002–2011. *MSMR*. 2012;**19**(10):7–10.
4. Golden SH, Brown A, Cauley JA, et al. Health disparities in endocrine disorders: biological, clinical, and nonclinical factors–an Endocrine Society scientific statement. *J Clin Endocrinol Metab*. 2012;**97**(9):E1579–E1639.
5. Jones DW. New Zealand Views on Goitre. *Proc R Soc Med*. 1928;**21**(7):1217–1230.
6. Brownlie BE, Wells JE. The epidemiology of thyrotoxicosis in New Zealand: incidence and geographical distribution in north Canterbury, 1983-1985. *Clin Endocrinol (Oxf)*. 1990;**33**(2):249–259.
7. Reid P, Robson B. Understanding health inequities. In: Robson B, Harris R, eds. *Hauora: Māori Standards of Health IV. A Study of the Years 2000–2005*. Wellington, New Zealand: Te Rōpū Rangahau Hauora a Eru Pōmare, 2007.
8. Tamatea JA, Conaglen JV, Elston MS. Response to radioiodine therapy for thyrotoxicosis: disparate outcomes for an indigenous population. *Int J Endocrinol*. 2016;**2016**:7863867.
9. Simmonds S, Robson B, Cram F, Purdie G. Kaupapa Māori epidemiology. *Australas Epidemiol*. 2008;**15**(1):3.
10. *Health Funds Association of New Zealand*. Annual Review 2015. Secondary Annual Review 2015 2015. https://www.healthfunds.org.nz
11. Statistics New Zealand. Statistical Standard for ethnicity. http://archive.stats.govt.nz/methods/classifications-and-standards/classification-related-stats-standards/ethnicity.aspx. Wellington, New Zealand: Statistics New Zealand, 2010:1–11.

12. Cormack D, Harris R. *Issues in Monitoring Māori Health and Ethnic Disparities: An Update*. Wellington, New Zealand: Te Rōpū Rangahau Hauora a Eru Pōmare, 2009:1–48.
13. Aitkinson J, Salmond CE, Crampton P. *NZDep2013 Index of Deprivation*. Wellington, New Zealand: Department of Public Health, University of Otago, 2014. https://www.otago.ac.nz/wellington/departments/publichealth/research/hirp/otago020194.html
14. Salmond C, Crampton P, King P, Waldegrave C. NZiDep: a New Zealand index of socioeconomic deprivation for individuals. *Soc Sci Med*. 2006;**62**(6):1474–1485.
15. Crooks J, Murray IP, Wayne EJ. Statistical methods applied to the clinical diagnosis of thyrotoxicosis. *Q J Med*. 1959;**28**(110):211–234.
16. World Health Organization. Assessment of iodine deficiency disorders and monitoring their elimination: A guide for programme managers. 3rd ed, 2007:Annex 2, Method for determining thyroid size by ultrasonography. https://apps.who.int/iris/bitstream/handle/10665/43781/9789241595827_eng.pdf.
17. Caruso G, Attard M, Caronia A, Lagalla R. Color Doppler measurement of blood flow in the inferior thyroid artery in patients with autoimmune thyroid diseases. *Eur J Radiol*. 2000;**36**(1):5–10.
18. Public Health England. Analytical Tools for Public Health: Commonly used public health statistics and their confidence interval. https://fingertips.phe.org.uk/profile/guidance. Association of Public Health England, 2008.
19. Ahmad O, Boschi-Pinto C, Lopez AD, Murray CJL, Lozano R, Inoue M. Age Standardization of Rates: A New WHO Standard. GPE Discussion Paper Series. https://www.who.int/healthinfo/paper31.pdf. World Health Organization, 2001:**14**.
20. Segi M. *Cancer mortality for selected sites in 24 countries (1950–1957)*. Sendai, Japan: Department of Public Health, Tohoku University of Medicine, 1960.
21. Robson B, Purdie G, Cram F, Simmonds S. Age standardisation - an indigenous standard? *Emerg Themes Epidemiol*. 2007;**4**:3.
22. Kalk WJ. Thyrotoxicosis in urban black Africans: a rising incidence. *East Afr Med J*. 1981;**58**(2):109–116.
23. Boelaert K, Torlinska B, Holder RL, Franklyn JA. Older subjects with hyperthyroidism present with a paucity of symptoms and signs: a large cross-sectional study. *J Clin Endocrinol Metab*. 2010;**95**(6):2715–2726.
24. Laurberg P, Buchholtz Hansen P, Iversen E, Eskjaer Jensen S, Weeke J. Goitre size and outcome of medical treatment of Graves' disease. *Acta Endocrinol. (Burchar)* 1986;**1986**(111):1.
25. Kalk WJ. Atypical features of hyperthyroidism in blacks. *S Afr Med J*. 1980;**57**(17):707–710.
26. Kuo LE, Simmons KD, Wachtel H, et al. Racial disparities in initial presentation of benign thyroid disease for resection. *Ann Surg Oncol*. 2016;**23**(8):2571–2576.
27. Freire-Maia DV, Freire-Maia A. Endemic goitre in whites and negroes: racial or social effect? *Trop Geogr Med*. 1981;**33**(4):387–392.
28. Hegedüs L. Thyroid size determined by ultrasound. Influence of physiological factors and non-thyroidal disease. *Dan Med Bull*. 1990;**37**(3):249–263.
29. Wilson S, Parle JV, Roberts LM, et al.; Birmingham Elderly Thyroid Study Team. Prevalence of subclinical thyroid dysfunction and its relation to socioeconomic deprivation in the elderly: a community-based cross-sectional survey. *J Clin Endocrinol Metab*. 2006;**91**(12):4809–4816.
30. Olmos RD, Figueiredo RC, Aquino EM, Lotufo PA, Bensenor IM. Gender, race and socioeconomic influence on diagnosis and treatment of thyroid disorders in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Braz J Med Biol Res*. 2015;**48**(8):751–758.
31. Harris R, Cormack D, Tobias M, et al. The pervasive effects of racism: experiences of racial discrimination in New Zealand over time and associations with multiple health domains. *Soc Sci Med*. 2012;**74**(3):408–415.
32. Radosavljević VR, Janković SM, Marinković JM. Stressful life events in the pathogenesis of Graves' disease. *Eur J Endocrinol*. 1996;**134**(6):699–701.
33. Vestergaard P. Smoking and thyroid disorders–a meta-analysis. *Eur J Endocrinol*. 2002;**146**(2):153–161.
34. Robson B, Robson C, Harris R, Purdie G. Hospitalisations. In: Robson B, Harris R, eds. *Hauora: Māori Standards of Health IV. A Study of the Years 2000–2005*. Wellington, New Zealand: Te Rōpū Rangahau Hauora a Eru Pōmare, 2007.
35. Tamatea JAU, Tu'akoi K, Meyer-Rochow GY, Conaglen JV, Elston MS. Inequitable long-term outcomes for an indigenous population after definitive treatment of patients with Graves disease. *J Endocr Soc*. 2019;**3**(7):1335–1344.
36. Hercus CE, Benson WN, Carter CL. Endemic goitre in New Zealand, and its relation to the soil-iodine: studies from the University of Otago, New Zealand. *J Hyg (Lond)*. 1925;**24**(3-4):321–402.3.

37. Mann JI, Aitken E. The re-emergence of iodine deficiency in New Zealand? *N Z Med J*. 2003;**116**(1170):U351.
38. Food Standards Australia New Zealand (FSANZ). *Final assessment report—proposal P230: consideration of mandatory fortification with iodine for New Zealand*. https://www.foodstandards.govt.nz/code/proposals/documents/P230_FAR_Attach_1_6___12_13.pdf. Wellington, New Zealand, 2008.
39. *Ministry of Health New Zealand. Iodine. Secondary Iodine* 2010. https://www.health.govt.nz/your-health/healthy-living/food-activity-and-sleep/healthy-eating/iodine
40. Edmonds JC, McLean RM, Williams SM, Skeaff SA. Urinary iodine concentration of New Zealand adults improves with mandatory fortification of bread with iodised salt but not to predicted levels. *Eur J Nutr*. 2016;**55**(3):1201–1212.