

Epidemiology

# Patients on levothyroxine replacement in the community: association between hypothyroidism symptoms, co-morbidities and their quality of life

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## Abstract

**Introduction.** Patients may be symptomatic, resulting in lower quality of life (QOL), despite L-thyroxine (LT4) therapy for hypothyroidism or having normal thyroid function. We hypothesized that their clinical symptoms of hypothyroidism and co-morbidities were associated with QOL.

**Objective.** The study aimed to determine the association between the hypothyroid-related symptoms of Asian patients on LT4 treatment, their co-morbidities and their QOL.

**Method.** A questionnaire survey was conducted from November 2015 to July 2016 on consecutive multi-ethnic Asian patients on LT4 treatment for their hypothyroidism in a public primary care clinic in Singapore. Data on their demography, clinical symptoms, morbidity status, QOL scores based on the EQ5D instrument and thyroid function tests were computed and analysed, including logistic regression analysis to identify factors associated with lower QOL.

**Results.** Complete data of 226 Asian patients (79.0% women; 74.2% Chinese, 10.0% Malay, 13.1% Indian and 2.6% other minority groups; median age 57 years; 27.5% had previous thyroid surgery) were analysed. Their QOL was not associated with their socio-demographic profiles, clinical parameters and latest thyroid-stimulating hormone and free thyroxine levels. Patients reporting weight gain, dry or coarse skin, leg swelling, feeling weak and carpal tunnel syndrome had significantly lower QOL; 53.6% of them with any single symptom had lower QOL. More patients had lower QOL if they had two or more symptoms and multiple medical conditions.

**Conclusion.** In Asian patients with hypothyroidism, weight gain, feeling tired, feeling weak, having dry or coarse skin, leg swelling and increased number of co-morbidities and symptoms were significantly associated with poorer QOL.

**Key words:** Co-morbidities, deficiency, health care, primary hyperthyroidism, therapy, thyroid function test, thyroid-stimulating hormone.

## Introduction

Patients with known hypothyroidism are often assessed by their physicians via history taking to identify related clinical symptoms. This is often accompanied by a thyroid function test, comprising free thyroxine (FT4) and thyroid-stimulating hormone (TSH), to define the thyroid status. Patients are usually treated with L-thyroxine (LT4) replacement therapy, which aims to resolve symptoms of hypothyroidism, normalize serum TSH and improve quality of life (QOL) (1). However, studies have shown achieving a state of biochemical euthyroidism, which can be difficult under normal circumstances. A proportion of patients can be either over- or under-treated with LT4 replacement therapy due to various factors, including demographic characteristics, medication adherence and complexities of treatment regimens. Our own data suggest that 40.2% of patients do not meet biochemical euthyroidism, with levels of their FT4 and TSH within the laboratory's stipulated range (2).

Once the patients are started on their LT4 therapy, their symptoms are expected to resolve and their general well-being will be restored (3). However, a recent multi-centre randomized controlled trial on older patients with subclinical hypothyroidism treated with LT4 therapy showed no benefits in hypothyroid symptoms and tiredness scores in a thyroid-related QOL questionnaire (4). In addition, a subset of patients does not feel well after taking LT4, despite having a normal serum TSH level (5). Paterson *et al.* showed that significant proportions of patients were not satisfied with their LT4 treatment in their large telephone survey of over 12 000 subjects (6). Investigators attributed it to lower triiodothyronine (T3) levels, but combination LT4/LT3 (liothyronine) therapy has not definitively shown to improve symptoms from a review of 14 trials (7). Although combination of levothyroxine (LT4) and liothyronine (LT3) had not convincingly shown to be superior to LT4 alone, some studies had demonstrated improved QOL on the combination therapy (8). Hennessey and Espallat came to the same conclusion on combined L4/LT3 treatment in a more recent report. They urged physicians to further investigate patients with persistent symptoms despite being biochemically euthyroid with LT4 monotherapy (9).

Inevitably, persistent symptoms adversely affect patients' well-being and activities of daily living. This outcome is often assessed in multiple dimensions to produce an aggregated outcome to reflect their QOL (10). QOL is the general well-being of individuals and encompasses life satisfaction in various domains, ranging from physical health, family, education, employment, wealth, religious beliefs, finance and environment. One of the ways we can assess patients' QOL is by questionnaire-based instruments, which can be disease specific or general well-being. While thyroid-specific QOL instruments are available, they are often not validated in specific populations whose native tongue is different from the language used in the instrument (11). They have specific psychometric properties, strength and weaknesses, such that their selection becomes a challenge (12). Moreover, it is not practical in general practice setting to assess patients with a wide spectrum of diseases using disease-specific QOL instruments. Patients with hypothyroidism often have co-morbidities, which may also impact on their QOL (2). Thus, a generic instrument measuring QOL for this group of patients may be more apt for holistic management in primary care.

Patients with hypothyroidism may have multiple symptoms despite LT4 therapy, which have variable impact on their QOL. McMillan *et al.* showed that British patients with hypothyroidism were more bothered by symptoms such as hair problems, weight gain, depression, cold and tiredness when evaluated using disease-specific QOL and symptoms questionnaires (10). Forty-three per cent of their study population were

from a hospital clinic, which tended to treat more complicated cases, such as secondary hypothyroidism or those with other concomitant endocrine conditions. However, majority of their patients were treated in primary care; their symptoms may be mild and their impact on their QOL remains unclear, especially those with multiple morbidities. It is also presumptive that the presence of multiple hypothyroidism-related symptoms amongst these patients would further aggravate their QOL. With current uncertainty in the appropriate level of thyroxine replacement based on thyroid function test (13), relieving their symptoms and improving their QOL are pragmatic goals for the titration of the thyroxine replacement doses. There is thus a need for better understanding of the relationship between symptomatology and QOL in patients with hypothyroidism in the community.

Therefore, we postulated that the QOL of patients with hypothyroidism, treated with LT4 therapy alone, would be inversely associated with the increasing physical symptoms and co-morbidities. Therefore, the objective of the study was to determine the QOL of patients on LT4 therapy for hypothyroidism in general practice and its association with their demography, clinical symptomatology and morbidity status.

## Methods

The study comprised of an assisted questionnaire survey that was administered to patients with hypothyroidism on LT4 therapy during their medical consultation at a typical public primary care clinic (polyclinic).

### Study site

The local Asian population is served by 20 polyclinics when they access public health care services in Singapore. The study was carried out in one such polyclinic, located in an estate situated in the north-eastern region of the island state. As a branch of SingHealth Polyclinics, an academic primary care institution, the study site serves a population of 137 500 residents, comprising 67.3% Chinese, 20.3% Malay and 8.3% Indian ethnic groups (2). LT4 tablets are dispensed within the polyclinic in-house pharmacy (Euthyrox by Merck Serono) at subsidized rates.

### Subjects

The target subjects were multi-ethnic adult Asian patients with primary hypothyroidism as evidenced from the diagnosis code in their electronic medical records. They were currently treated with levothyroxine replacement therapy for a minimum period of 6 months based on their electronic prescriptions. Patients with secondary hypothyroidism were excluded in the study. They should be able to provide informed consent without impairment from visual-, auditory- and cognitive-related medical conditions.

### Sample size calculation

This study is a subanalysis of the original study to determine the thyroid function status in Asian patients with primary hypothyroidism on levothyroxine replacement therapy. Based on the study by Okosieme *et al.* (14) which reported that 17.4% of patients were inadequately replaced with LT4, the sample size was computed to be 217 subjects, with an error margin of 5%. To allow for an estimation of 5% dropout and missing data, the investigators targeted 230 eligible subjects for recruitment.

### Patient recruitment and procedure

Potential subjects were identified during their medical review with the polyclinic physicians at the study site or when they had thyroid

function investigations at the polyclinic in-house laboratory. They were briefed by the investigators on the study procedure using the approved participant information leaflet. Their diagnosis and LT4 treatment were verified by the investigator from their electronic medical records and prescriptions before obtaining their written informed consent.

The subjects were assisted in filling the English-based questionnaire, with translation from the investigators whenever necessary. Next, their weight, body mass index (BMI), systolic and diastolic pressures and heart rates were measured using calibrated instruments at the study site. Their latest laboratory investigations, including their thyroid function tests, were retrieved from their respective electronic medical records.

The Clinical Biochemistry laboratory in the Department of Clinical Pathology at Singapore General Hospital carried out the

thyroid function tests using the Beckman Coulter Unicel Dxl 800 immunoassay analyzer. The coefficients of variation for the assays were 3.6% and 5.5% for FT4 and TSH, respectively. The calibration of the test was performed every 28 days based on the manufacturer's recommendation. A courier service transferred the blood specimens from the polyclinic study site to the hospital laboratory twice during weekdays and once during Saturdays.

The data were then coded and entered into an Excel spread sheet, which was then audited by the data management officer. The dataset was anonymised before it was passed to the biostatistician for statistical analysis.

### Questionnaire

Information on the demographic profiles, concomitant medical conditions, clinical symptoms of the hypothyroidism and the

**Table 1.** Baseline characteristics of 229 study participants with primary hypothyroidism, 2015–2016

	Total	Low EQ5D <sup>a</sup>	High EQ5D <sup>a</sup>
Total (%)	229 (100.0)	114 (49.8)	115 (50.2)
Demographics			
Gender (%)			
Male	48 (21)	19 (39.6)	29 (60.4)
Female	181 (79)	95 (52.5)	86 (47.5)
Ethnic group (%)			
Chinese	170 (74.2)	80 (47.1)	90 (52.9)
Malays	23 (10)	13 (56.5)	10 (43.5)
Indian	30 (13.1)	18 (60)	12 (40)
Eurasian/others	6 (2.6)	3 (50)	3 (50)
Age, median (IQR)	57 (50.5–67)	59 (51–68)	57 (50–67)
Marital status (%)			
Married	182 (79.5)	85 (46.7)	97 (53.3)
Single/divorced/widowed/separated	47 (20.5)	29 (61.7)	18 (38.3)
Education (%)			
No formal education/primary	57 (24.9)	24 (42.1)	33 (57.9)
Secondary	92 (40.2)	54 (58.7)	38 (41.3)
Post-secondary and above	80 (34.9)	36 (45)	44 (55)
Housing (%)			
Public housing (1–5 room)	151 (65.9)	77 (51)	74 (49)
Private housing (HUCD flat, studio apartment, condominium, landed property)	78 (34.1)	37 (47.4)	41 (52.6)
Weight, median (IQR)	62.4 (55.8–71.3)	63.3 (55.8–74.4)	61.3 (54.9–68.4)
BMI, median (IQR)	25.1 (22.2–27.9)	25.5 (22.4–29.4)	24.3 (21.9–27.5)
Had previous thyroid surgery (%)			
Yes	63 (27.5)	35 (55.6)	28 (44.4)
No	166 (72.5)	79 (47.6)	87 (52.4)
Clinical parameters			
Pulse rate, mean (SD)	70 (62–78)	71.5 (64.8–80)	68 (62–78)
Systolic blood pressure, mean (SD)	127 (114–142.5)	126 (112–140.3)	129 (116–145)
Diastolic blood pressure, mean (SD)	70 (64–78)	69.5 (63–78)	72 (66–80)
Laboratory investigation			
Latest TSH level (mU/L), median (IQR)	2.5 (1.3–3.9)	2.4 (1.3–3.7)	2.5 (1.2–4.1)
Number of thyroid function tests in last 12 months, median (IQR)	3 (2–4)	3 (2–4)	3 (2–4)
Latest FT4 level (pmol/L), median (IQR)	12.7 (11.4–14.6)	12.8 (11–14.6)	12.6 (11.6–14.6)
Fasting blood glucose, median (IQR)	5.3 (4.9–5.9)	5.4 (5,6)	5.3 (4.9–5.9)
Total cholesterol, mmol/L, mean (SD)	4.8 (0.9)	4.8 (0.9)	4.8 (0.9)
HDL, mmol/L, mean (SD)	1.5 (0.4)	1.5 (0.4)	1.5 (0.4)
LDL, mmol/L, mean(SD)	2.7 (0.8)	2.7 (0.8)	2.8 (0.8)
Triglyceride, mmol/L, mean(SD)	1.3 (0.5)	1.3 (0.5)	1.3 (0.6)

BMI, body mass index; TSH, thyroid-stimulating hormone; FT4, free thyroxine; HDL, high-density lipoproteins; LDL, low-density lipoproteins; IQR, interquartile range.

<sup>a</sup>EQ5D index scores are defined based on its median value such that high EQ5D—EQ5D index score  $\geq 0.78$ , low EQ5D—EQ5D index score  $< 0.78$ .

**Table 2.** EQ5D index with thyroid symptoms, co-morbidities and combination of symptoms and co-morbidities, 2015–2016

	EQ5D index <sup>a</sup>		Crude OR (95% CI)	P-Value
	Low EQ5D, n (%)	High EQ5D, n (%)		
<b>Thyroid symptoms</b>				
Weight gain			2.98 (1.74–5.1)	<0.01*
Yes	72 (63.2)	42 (36.8)		
No	42 (36.5)	73 (63.5)		
Feeling cold			1.51 (0.89–2.56)	0.126
Yes	53 (55.8)	42 (44.2)		
No	61 (45.5)	73 (54.5)		
Feeling tired			2.55 (1.43–4.55)	<0.01*
Yes	89 (57.1)	67 (42.9)		
No	25 (34.2)	48 (65.8)		
Feeling weak			2.77 (1.62–4.72)	<0.01*
Yes	70 (62.5)	42 (37.5)		
No	44 (37.6)	73 (62.4)		
Constipation			2.03 (1.17–3.51)	0.011
Yes	50 (61)	32 (39)		
No	64 (43.5)	83 (56.5)		
Dry skin/coarse skin			2.69 (1.57–4.61)	<0.01*
Yes	76 (60.8)	49 (39.2)		
No	38 (36.5)	66 (63.5)		
Coarse hair			1.1 (0.63–1.9)	0.743
Yes	39 (51.3)	37 (48.7)		
No	75 (49)	78 (51)		
Leg swelling			2.39 (1.26–4.53)	0.01*
Yes	35 (66)	18 (34)		
No	79 (44.9)	97 (55.1)		
Any one or more symptom			10.39 (2.35–45.92)	<0.01*
Yes	112 (53.6)	97 (46.4)		
No	2 (10)	18 (90)		
Any two or more symptoms			4.3 (2.15–8.6)	<0.01*
Yes	101 (57.7)	74 (42.3)		
No	13 (24.1)	41 (75.9)		
Any three or more symptoms			3.87 (2.22–6.75)	<0.01*
Yes	83 (63.8)	47 (36.2)		
No	31 (31.3)	68 (68.7)		
<b>Co-morbidities</b>				
Hypertension/high blood pressure			1.62 (0.96–2.76)	0.072
Yes	54 (56.8)	41 (43.2)		
No	60 (44.8)	74 (55.2)		
High cholesterol			1.68 (0.99–2.83)	0.053
Yes	70 (55.6)	56 (44.4)		
No	44 (42.7)	59 (57.3)		
Type 2 diabetes mellitus			1.83 (0.85–3.94)	0.121
Yes	20 (62.5)	12 (37.5)		
No	94 (47.7)	103 (52.3)		
Heart attack			0.33 (0.03–3.22)	0.622
Yes	1 (25)	3 (75)		
No	113 (50.2)	112 (49.8)		
Stroke			1.71 (0.4–7.34)	0.499
Yes	5 (62.5)	3 (37.5)		
No	109 (49.3)	112 (50.7)		
Kidney disease			4.15 (0.46–37.67)	0.213
Yes	4 (80)	1 (20)		
No	110 (49.1)	114 (50.9)		
Carpal tunnel syndrome			3.48 (1.42–8.56)	0.004*
Yes	21 (75)	7 (25)		
No	93 (46.3)	108 (53.7)		
Any one or more co-morbidity			1.88 (1.07–3.31)	0.027*
Yes	85 (54.8)	70 (45.2)		
No	29 (39.2)	45 (60.8)		
Any two or more co-morbidities			1.69 (0.99–2.87)	0.053
Yes	54 (57.4)	40 (42.6)		
No	60 (44.4)	75 (55.6)		

Table 2. Continued

	EQ5D index*		Crude OR (95% CI)	P-Value
	Low EQ5D, n (%)	High EQ5D, n (%)		
Any three or more co-morbidities			2.41 (1.15–5.08)	0.018*
Yes	25 (67.6)	12 (32.4)		
No	89 (46.4)	103 (53.6)		
Combinations of symptoms and co-morbidities				<0.01*
0 to 2 symptoms + 0 to 2 co-morbidities	26 (29.5)	62 (70.5)	1	
0 to 2 symptoms + 3 or more co-morbidities	5 (45.5)	6 (54.5)	1.99 (0.56–7.09)	
3 or more symptoms + 0 to 2 co-morbidities	63 (60.6)	41 (39.4)	3.66 (2–6.7)	
3 or more symptoms + 3 or more co-morbidities	20 (76.9)	6 (23.1)	7.95 (2.86–22.06)	

CI, confidence interval; OR, odds ratio.

\*EQ5D index scores are defined based on its median value such that high EQ5D—EQ5D index score  $\geq 0.78$ , low EQ5D—EQ5D index score  $< 0.78$ .

\* refers to  $P$ -value  $< 0.05$ .

EQ-5D-5L instrument were captured in the questionnaire. Apart from 'none' in the reporting of physical symptoms, patients who indicated 'rarely' to 'more frequent occurrences' were classified as 'having physical symptoms'.

EQ-5D-5L is a tool that has been validated for QOL assessment in Singapore. It also included a visual analogue scale for a personal overall assessment of the individual QOL. According to the EQ-5D-5L User Guide (8, 15), the EQ-5D-5L states are converted to index value using EQ-5D-5L Crosswalk Index Value Calculator from the EuroQol website.

#### Laboratory range of thyroid function test

Normal range for TSH is from 0.65 to 3.70 mU/L, and normal range for FT4 is from 8.8 to 14.4 pmol/L.

#### Statistical analysis

EQ5D index scores are defined based on its median value in this study sample: high EQ5D indicates EQ5D index score of  $\geq 0.78$  and low EQ5D indicates EQ5D index score of  $< 0.78$ . The analysis included those that were under the categories as mentioned above. Forty-six cases were excluded as they did not fall under the defined categories. ANOVA or Kruskal–Wallis test was used to compare the difference in LT4 replacement therapy with the continuous demographics and clinical indicators, while chi-square or Fisher's Exact test was used for the categorical variables. Mann–Whitney  $U$ -test and independent  $t$ -test were performed to test the number of symptoms with EQ5D index value. All analyses were done using IBM SPSS Statistics, version 23.0. A  $P$ -value of 0.05 was considered significant.

#### Ethics approval

The SingHealth Centralized Institution Review Board approved the study (CIRB 2015/2891). The study was conducted from November 2015 to July 2016.

#### Results

As shown in Table 1, 229 Asian subjects were included in the analysis. The subjects comprised 79.0% women, 74.2% Chinese, 10.0% Malay, 13.1% Indian and 2.6% other minority ethnic groups. They had a median age of 57 years [interquartile range (IQR) 50.5–67.0 years] with 79.5% of them being married, 65.1% had up to

secondary education and 65.9% were living in public housing. Amongst the study population, 27.5% had previous thyroid surgery. There were no statistical differences between patients of low and high QOL based on EQ5D scores in their socio-demographic profiles, clinical parameters such as weight, BMI, pulse rate, systolic and diastolic blood pressures and laboratory investigations such as their latest levels of TSH, FT4, fasting blood glucose, total cholesterol, high-density lipoproteins -cholesterol, low-density lipoproteins-cholesterol and triglycerides.

As shown in Table 2, more patients with these symptoms alone, such as weight gain, constipation, dry or coarse skin, leg swelling, felt tired and weak, had significantly lower QOL; 53.6% of patients with any one symptom had lower QOL. The proportions of patients with lower QOL increased if they had two or more symptoms. More patients with carpal tunnel syndrome (CTS) had lower QOL than those without the condition. There were no statistical differences in patients with low or high QOL, if they had other single co-morbidity such as hypertension, hypercholesterolemia, type 2 diabetes mellitus, coronary and cerebrovascular diseases. Higher proportion of patients with increasing number of co-morbidities had lower QOL. Significantly, more patients with increasing number of symptoms and co-morbidities had lower QOL.

As evidenced in Table 3 Logistic regression analysis showed that weight gain, feeling weak, having dry or coarse skin and CTS increased the odd ratio of poor QOL. Figure 1 showed that the QOL was not associated with the thyroid function of the study population in terms of their TSH and FT4 levels.

#### Discussion

##### Summary

The QOL of patients with hypothyroidism was affected by their thyroid-specific and systematic symptoms, being inversely associated with their number of symptoms and co-morbidities. Determining the QOL of these patients using a generic assessment instrument may be an alternative, patient-centric decision-support tool for GPs to titrate their LT4 dosages in general practice.

##### Strengths and limitations

Assessing the health status of patients with hypothyroidism based on the presence of their thyroid-related symptoms is usually part of



routine clinical evaluation by GPs. Up to now, GPs face the challenge of deciding on the adjustment of LT4 dosages in response to the various symptoms presented to them by the patients. The findings in this study extend our understanding beyond what is currently known about the association of symptoms and co-morbidities with the QOL status. GPs could proactively review the number of co-morbidities from the medical records and assess the symptom burden of their patients via detailed history taking, with a quick check for their QOL using suitable instrument during the medical consultation. This approach will serve as prompts to check the adequacy of LT4 replacement and to explore other causes of persistent symptoms, such as interference from other concomitant drug therapy. Whilst earlier study reported the relationship between symptoms and QOL, the symptoms were intrinsic questions within the QOL instrument. The use of a generic instrument provides independent assessment of the symptoms in association with QOL. In addition, it also allows the evaluation of the impact of co-morbidities on the QOL, which is a more holistic indicator of the disease burden faced by patients with hypothyroidism.

The study centred on the multi-ethnic Asian patients with hypothyroidism, which limits its generalizability to Caucasian and other population. Nonetheless, the results did not reveal any ethnic differences of the patients in association with their QOL (Table 1).

**Table 3.** Logistic regression on factors influencing EQ5D index, 2015–2016

Thyroid symptoms and co-morbidities	Adjusted OR (95% CI)	P-Value
Weight gain (Yes)	3.12 (1.71–5.68)	<0.01*
Feeling tired (Yes)	1.28 (0.62–2.64)	0.507
Feeling weak (Yes)	2.12 (1.09–4.11)	0.027*
Dry skin/coarse skin (Yes)	2.27 (1.24–4.14)	0.008
Leg swelling (Yes)	1.40 (0.67–2.92)	0.365
Hypertension/high blood pressure (Yes)	1.60 (0.83–3.1)	0.164
High cholesterol (Yes)	0.99 (0.52–1.93)	0.992
Carpal tunnel syndrome (Yes)	3.05 (1.09–8.52)	0.034*
Type II DM (Yes)	1.55 (0.6–3.99)	0.362
Kidney disease (Yes)	1.06 (0.09–12.36)	0.965

CI, confidence interval; DM, diabetes mellitus; OR, odds ratio.  
\* refers to P-value < 0.05.

### Comparison with existing literature

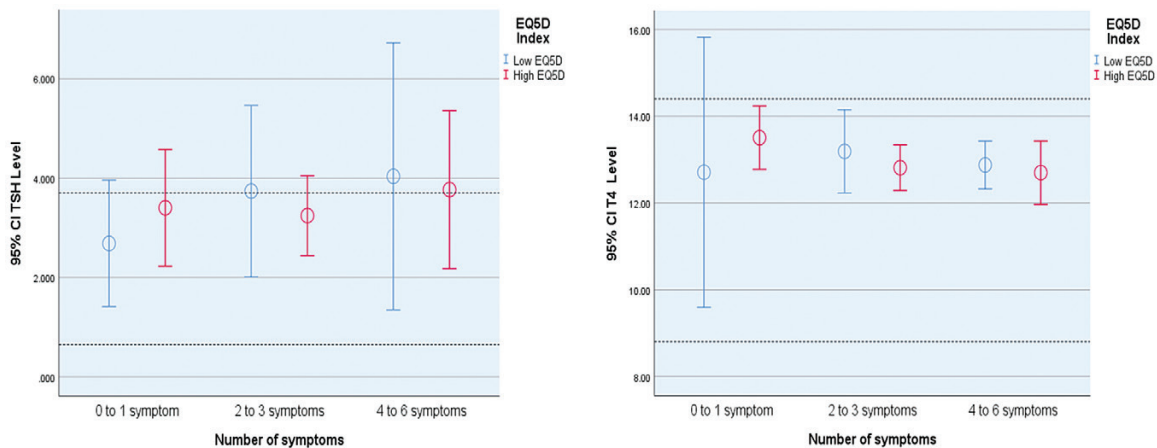
The results are compatible with the findings from other studies, which also reported the lack of relationship between serum FT4 and TSH levels and the QOL score of patients with hypothyroidism. Adding on the thyroid function test does not necessarily facilitate decision making as biochemical euthyroidism is often not attained by patients with hypothyroidism, despite LT4 therapy. Earlier study had also shown that the biochemical euthyroidism was not associated with better QOL (4).

The logistic regression analysis showed that the QOL of the study population were affected more by weight gain and cutaneous symptoms, similar to what was found in the British patients. The latter were also affected by cold intolerance and tiredness. In contrast, the Asian patients in this study were more likely to associate feeling weak with poorer QOL, reflecting on possible cultural influences in their perception and interpretation of subjective symptoms. Cold intolerance may be less of a bother to the local patients living in a tropical environment. Understanding which combination of symptoms affects a patient's QOL most significantly could aid physician's decision making before adjusting the dosage of thyroxine replacement.

The study showed the adverse effect of CTS on the QOL. It is based on the diagnosis list in the electronic health records of the patients. No nerve conduction test was carried out during the study to verify the CTS. In addition, a meta-analysis reported only modest association between hypothyroidism and CTS (16). It attributed confounding factors and publication bias to the association between the two diseases entities from the 18 studies included in the meta-analysis.

### Implications for research and/or practice

QOL assessment of patients is often used in research but is seldom conducted in routine clinical practice. The study suggests the possibility of developing an algorithm-based matrix to estimate the QOL of Asian patients on LT4 therapy for hypothyroidism. Referring to the results in Table 2, the proposed matrix would enable the physicians to compute the number and types of symptoms, and co-morbidities of their patients to predict the latter's QOL status. Such a matrix will require further validation study to determine its impact on the health outcomes of patients, including their QOL, and satisfaction of both patients and their health care providers.



**Figure 1.** TSH and freeT4 values at different levels of EQ5D with number of symptoms. EQ5D index scores are defined based on its median values such that high EQ5D—index score  $\geq 0.78$ , low EQ5D—index score < 0.78.

There is also great potential in the use of generic instruments, such as the EQ-5D-5L, to gauge treatment effectiveness in terms of QOL in patients suffering from various diseases. Incorporating routine QOL assessment will require implementation science to evaluate its effectiveness and efficiency during its translation in clinical practice and acceptance by the users.

## Conclusion

The study showed that the QOL of Asian patients on LT4 for hypothyroidism were affected by weight gain, feeling of weakness, dry and coarse skin and CTS. With increasing number of symptoms and co-morbidities, more of these patients would have lower QOL.

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## Declaration

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Ethics approval: Obtained for the study by the local research ethics committee, SingHealth Centralized Institution Review Board (CIRB 2015/2891).

Conflict of interest: None.

## References

- Guglielmi R, Frasoldati A, Zini M *et al.* Italian association of clinical endocrinologists statement-replacement therapy for primary hypothyroidism: a brief guide for clinical practice. *Endocr Pract* 2016; 22: 1319–26.
- Tan NC, Chew RQ, Koh YL *et al.* Primary hypothyroidism in the community: lower daily dosages of levothyroxine replacement therapy for Asian patients. *Medicine (Baltimore)* 2017; 96: e6145.
- Garber JR, Cobin RH, Gharib H *et al.*; American Association Of Clinical Endocrinologists And American Thyroid Association Taskforce On Hypothyroidism In Adults. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Thyroid* 2012; 22: 1200–35.
- David JS, Nicolas R, Patricia MK *et al.* Thyroid hormone therapy for older adults with subclinical hypothyroidism. *N Engl J Med* 2017; 376: 2534–44.
- Chakera AJ, Pearce SH, Vaidya B. Treatment for primary hypothyroidism: current approaches and future possibilities. *Drug Des Devel Ther* 2012; 6: 1–11.
- Peterson SJ, Cappola AR, Castro MR *et al.* An online survey of hypothyroid patients demonstrates prominent dissatisfaction. *Thyroid* 2018; 28: 707–21.
- Jonklaas J. Persistent hypothyroid symptoms in a patient with a normal thyroid stimulating hormone level. *Curr Opin Endocrinol Diabetes Obes* 2017; 24: 356–63.
- Dayan C, Panicker V. Management of hypothyroidism with combination thyroxine (T4) and triiodothyronine (T3) hormone replacement in clinical practice: a review of suggested guidance. *Thyroid Res* 2018; 11: 1.
- Hennessey JV, Espaillat R. Current evidence for the treatment of hypothyroidism with levothyroxine/levotriiodothyronine combination therapy versus levothyroxine monotherapy. *Int J Clin Pract.* 2018; 72: e13062.
- McMillan C, Bradley C, Razvi S, Weaver J. Evaluation of new measures of the impact of hypothyroidism on quality of life and symptoms: the ThyDQoL and ThySRQ. *Value Health* 2008; 11: 285–94.
- Razvi S, McMillan CV, Weaver JU. Instruments used in measuring symptoms, health status and quality of life in hypothyroidism: a systematic qualitative review. *Clin Endocrinol (Oxf)* 2005; 63: 617–24.
- Quinke EM, Villringer A, Kratzsch J, Karger S. Patient-reported outcomes in adequately treated hypothyroidism—insights from the German versions of ThyDQoL, ThySRQ and ThyTSQ. *Health Qual Life Outcomes* 2013; 11: 68.
- Klaver EI, van Loon HC, Stienstra R *et al.* Thyroid hormone status and health-related quality of life in the LifeLines Cohort Study. *Thyroid* 2013; 23: 1066–73.
- Okosieme O, Gilbert J, Abraham P *et al.* Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee. *Clin Endocrinol (Oxf)* 2016; 84: 799–808.
- EuroQol - User Guide [Internet]. <http://www.euroqol.org/about-eq-5d/publications/user-guide.htm> (accessed on 9 September 2016).
- Shiri R. Hypothyroidism and carpal tunnel syndrome: a meta-analysis. *Muscle Nerve* 2014; 50: 879–83.