

Competing interest

We are not aware of any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated. The authors have no conflicts of interest to be declared relevant to the data collection, analysis and interpretation.

Full session link:

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Subclinical Hypothyroidism Influences the Quality of Life During Pregnancy: Results From ThyPreQoL2020

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Background

- **Subclinical Hypothyroidism** (= increased TSH, normal FT4; SubHypo) affects ~3.5 % pregnant women¹
- SubHypo is associated with an ↑ risk of pre-eclampsia², gestational diabetes³, gestational hypertension⁴, placental abruption⁴, miscarriage⁴, preterm delivery^{5,6}, postpartum hemorrhage⁷, low birth weight⁷, and neonatal death^{4,8}
- There is a probable impact of SubHypo on the cognitive performance of offspring^{9,10,11}
- There has been a continuing debate for over 25 years on (1) whether a universal screening during pregnancy can improve these outcomes and (2) whether it is cost-effective^{12, 13}
- Significant new evidence has accumulated since the last models were published¹¹. Only a few risks can be decreased with hormonal substitution¹¹.
- While assessing the feasibility of building an updated Czech cost-utility model, we systematically reviewed the literature¹⁴ and found that, to date, none have described:
 - The generic quality of life (*i.e.*, models have relied on expert estimates of utilities)
 - Specific symptoms (*i.e.*, the targeted screening cannot be effectively done in everyday practice)

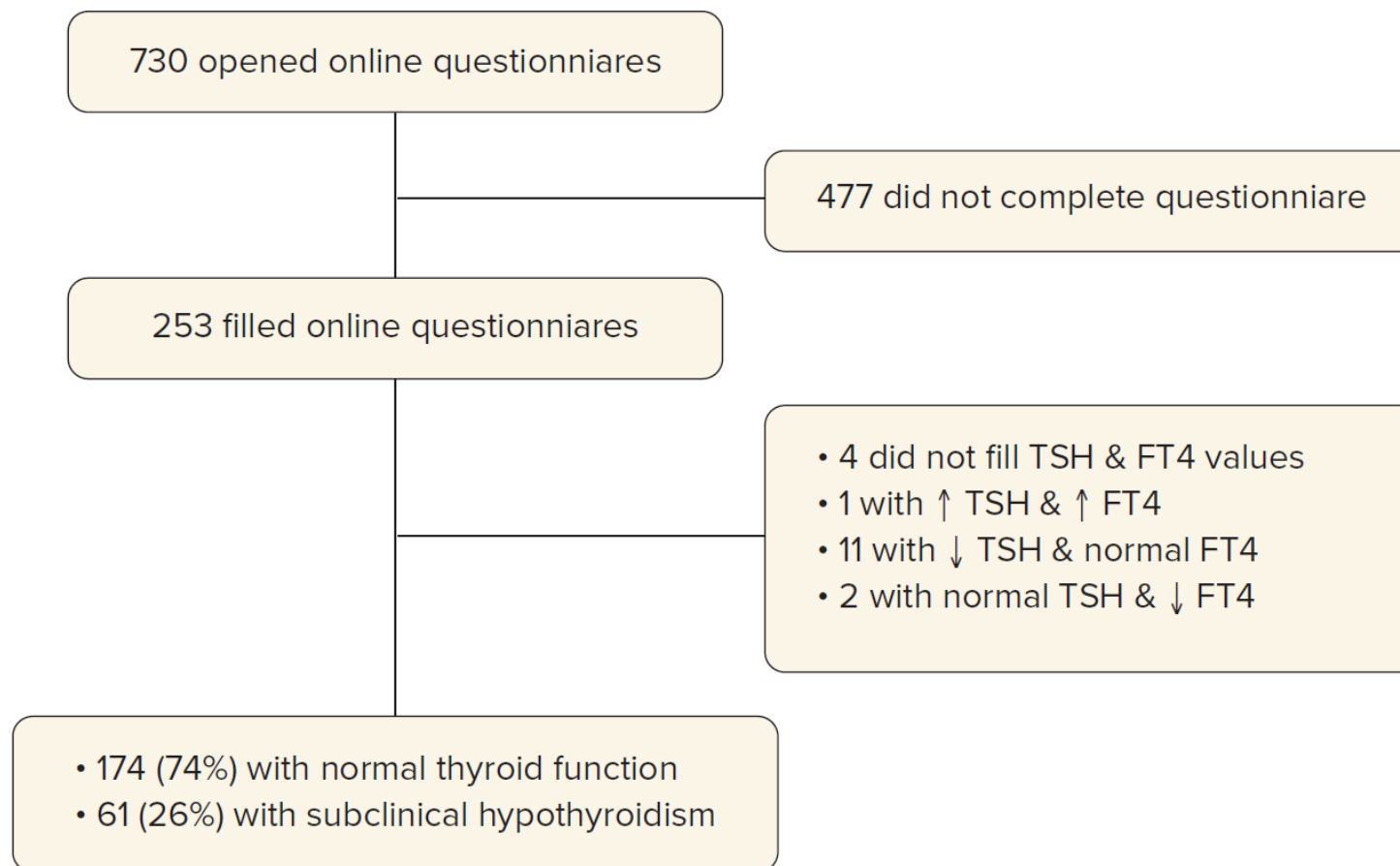
Design & Aims of ThyPreQoL2020

- Primary cross-sectional online questionnaire data collection (ThyPreQoL2020; NCT04167423)
- Screening test (TSH, FT4, anti-TPO antibodies)
- Generic QoL (EQ-5D 5L¹); Disease-specific QoL+ symptoms (ThyPRO-39²)
- Confounders³: age, week of pregnancy, parity, characteristics of previous labors, type of index conception, other comorbidities, education, abuses, regular physical activity/exercise, social and financial distress, emotional relationship to the index pregnancy, subjective perception of having supportive friends and family
- Conducted 2020 to 2022 in 14 hospital and ambulatory Ob-Gyn offices in 6 regions of the Czech Republic
- SubHypo was defined separately for each trimester according to
 - 2014 ETA Guideline⁴ (TSH)
 - Czech population reference ranges⁵ (FT4)
- Alternative SubHypo definition for sensitivity analysis (Czech reference ranges also for TSH)⁶

1. Janssen 2013; 2. Watt 2015; 3. Lagadec 2018; 4. Lazarus 2014; 5. Springer 2009; 6. Šálek 2018

The study was approved and supervised by the Ethics Committee of University Hospital Hradec Králové under identifier 201911S140

ThyPreQoL2020: Cohort description



ThyPreQoL2020: Cohort description

	Euthyroid (ETA 2014)	SubHypo (ETA 2014)	p-value
Number of women	174 (74%)	61 (26%)	
Age	30.94 ± 4.95	30.51 ± 5.92	0.290
TSH	1.48 ± 0.67	4.14 ± 1.40	<0.001
FT4	13.94 ± 1.88	13.93 ± 1.87	0.956
TPOAb positivity	111 (66%)	41 (69%)	0.593
Week of pregnancy	14.84 ± 6.48	14.00 ± 5.74	0.401
Primiparous	75 (43%)	38 (62%)	0.010
Previous caesarean section	24 (24%)	4 (17%)	0.482
Assisted reproduction (index pregnancy)	10 (6%)	6 (10%)	0.275
Other medical condition	17 (10%)	8 (13%)	0.466
Education basic	6 (3%)	3 (5%)	0.444
Education intermediate	72 (41%)	30 (49%)	0.444
Education university	96 (55%)	28 (46%)	0.444
Positive smoking history	71 (41%)	37 (61%)	0.007
Current smoker	10 (6%)	2 (3%)	0.451
Current alcohol consumer	14 (8%)	4 (7%)	0.707
Not using other substances	174 (100%)	61 (100%)	.
I am happy to be pregnant. This pregnancy is a positive event.	173 (99%)	60 (98%)	0.436
I am feeling financially or socially distressed.	4 (2%)	2 (3%)	0.676
I feel like I have good friends who can help me if I need it.	171 (99%)	58 (97%)	0.104
I feel like I have good family who can help me if I need it.	173 (99%)	60 (98%)	0.436
Weekly exercises/physical activity	2.48 ± 2.23	2.21 ± 2.17	0.388

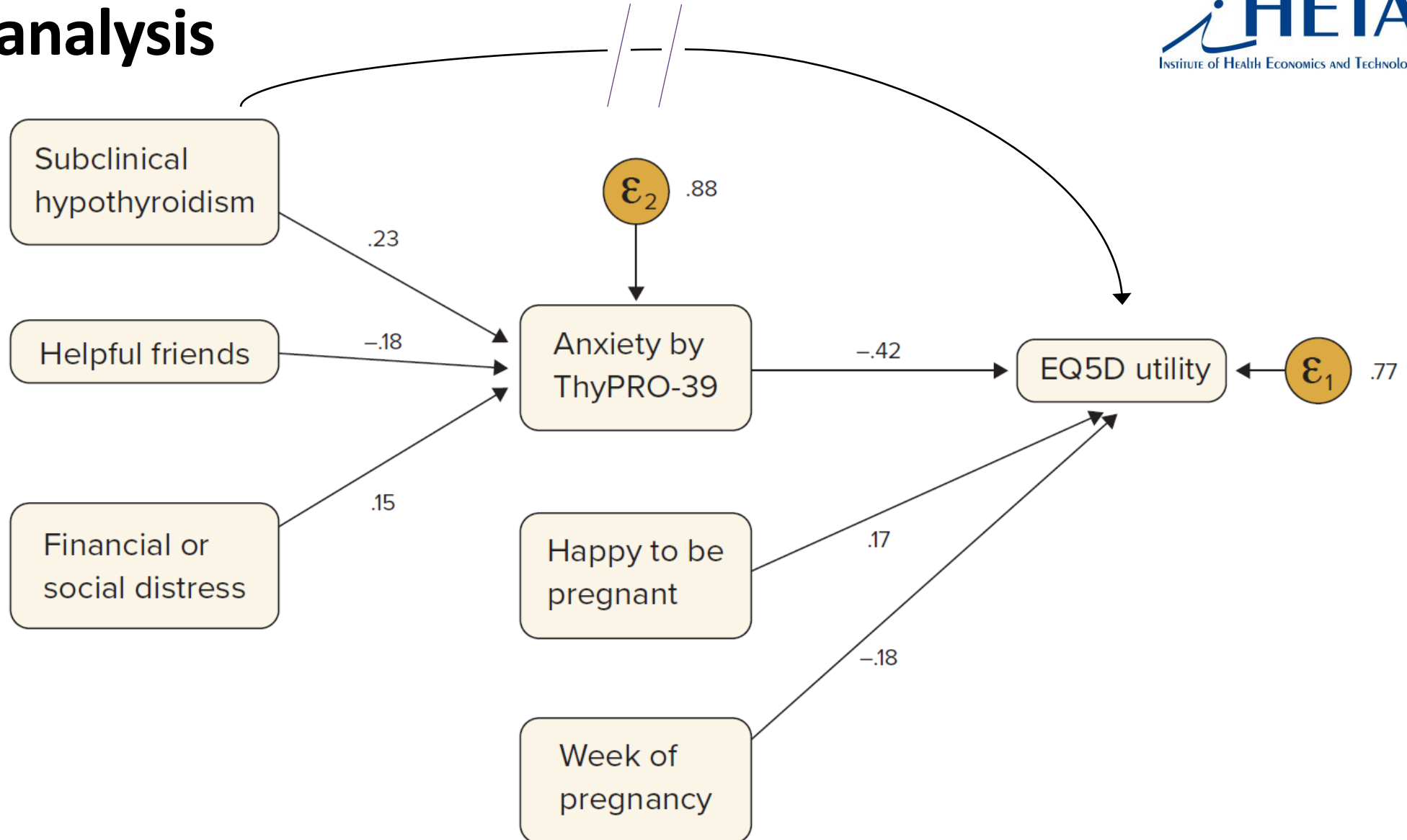


ThyPreQoL2020: Patient-reported Outcomes

	Euthyroid (ETA 2014)	SubHypo (ETA 2014)	p-value	Adjusted difference*	p-value
Number of pregnant women	174 (74%)	61 (26%)			
ThyPRO-39 scores	(mean ± SD)	(mean ± SD)		mean (confidence interval)	
Goitre symptoms	5.37 ± 7.91	6.98 ± 7.95	0.087	1.98 (-0.45 to 4.42)	0.111
Hyperfunction symptoms	13.26 ± 11.13	15.95 ± 12.10	0.057	1.74 (-1.84 to 5.32)	0.339
Hypofunction symptoms	15.05 ± 13.13	19.16 ± 15.22	0.023	3.19 (-1.12 to 7.52)	0.147
Eye symptoms	4.25 ± 6.75	7.97 ± 8.58	<0.001	3.97 (1.66 to 6.28)	0.001
Tiredness	41.86 ± 19.98	49.30 ± 21.52	<0.001	6.18 (-0.03 to 12.39)	0.051
Cognitive impairment	8.28 ± 12.41	12.98 ± 13.60	0.007	4.17 (0.13 to 8.21)	0.043
Anxiety	12.53 ± 13.50	22.08 ± 20.02	<0.001	9.38 (4.63 to 14.12)	0.000
Depression	21.42 ± 14.72	26.46 ± 14.42	0.011	3.70 (-0.84 to 8.23)	0.110
Emotional susceptibility	23.77 ± 15.95	29.28 ± 16.27	0.011	4.13 (-0.76 to 9.01)	0.098
Social life impairment	6.29 ± 12.60	9.38 ± 11.87	0.048	2.34 (-1.58 to 6.26)	0.240
Day life impairment	11.13 ± 15.21	12.56 ± 17.42	0.273	1.72 (-3.30 to 6.73)	0.501
Cosmetic complaints	3.49 ± 8.92	5.85 ± 12.10	0.054	2.05 (-1.00 to 5.10)	0.186
Composite score	17.76 ± 10.70	23.16 ± 12.23	<0.001	4.62 (1.15 to 8.10)	0.009
Overall impact on the quality of life	4.89 ± 12.80	7.38 ± 15.37	0.110	2.31 (-1.97 to 6.60)	0.289
EQ5D 5L scores	(mean ± SD)	(mean ± SD)		mean (confidence interval)	
Utility	0.92 ± 0.11	0.89 ± 0.12	0.028	-0.036 (-0.069 to -0.003)	0.033
VAS	86.66 ± 17.37	80.66 ± 27.61	0.025	-6.53 (-12.81 to -0.22)	0.043

*adjusted to for age, trimester, presence of AntiTPO, primiparity, other preceding health conditions, education level, and smoking history

Path analysis



Sensitivity analysis

SubHypo defined according to Czech population reference ranges:

- ThyPRO-39 Anxiety remains significantly more pronounced ($p = 0.002$, adjusted $p = 0.003$)
- ThyPRO-39 Composite score remains higher ($p = 0.012$, adjusted $p = 0.045$)
- EQ5D utility difference becomes even more significant (adjusted difference 0.057; $p = 0.005$)
- Path analysis shows 56% mediation through anxiety (complete mediation with $p = 0.020$)

	Euthyroid	SubHypo	p-value	Adjusted difference	p-value
Number of pregnant women	196 (84%)	37 (16%)			
ThyPRO-39 scores	mean \pm SD	mean \pm SD		mean (95% confidence interval)	
Anxiety	13.61 \pm 14.56	21.86 \pm 20.96	0.002	8.76 (3.00 to 14.51)	0.003
Composite score	18.49 \pm 10.86	23.06 \pm 13.74	0.012	4.32 (0.095 to 8.54)	0.045
EQ-5D-5L scores	mean \pm SD	mean \pm SD		mean (95% confidence interval)	
Utility	0.92 \pm 0.11	0.88 \pm 0.11	0.028	-0.057 (-0.096 to -0.017)	0.005

ThyPreQoL2020: Summary of the Results

- Euthyroid and SubHypo patients are comparable in most characteristics
- Euthyroid and SubHypo patients have different outcomes:
 - Eye symptoms, impaired cognition and increased anxiety (ThyPRO-39)
 - Small but measurable decrease in the QoL (EQ5D utility and VAS)
- SubHypo is the strongest predictor of anxiety (ThyPRO-39)
- Anxiety (ThyPRO-39) is the strongest predictor of QoL (EQ5D utility)
- 86% of the effect of SubHypo on the QoL is mediated via anxiety ($p = 0.001$)
- We found no other ways that SubHypo impacts the QoL during pregnancy

Limitations

- Long questionnaire = low response rate (~ 35%)
- The distance between test and questionnaire completion not known in ~50% subjects
- Initiation of hormonal substitution not reported consistently
- **Survey was not blinded = potential confounding by knowing the diagnosis
BUT blinding will not be done in the common practice**

Strengths

- The first use of the EQ-5D-5L and ThyPRO-39 during pregnancy
- Wide range of confounding factors collected and analyzed
- Both symptoms and QoL were collected in both euthyroid and SubHypo
- Data collected in the common practice setting
- The first evidence that SubHypo during pregnancy is associated with a decrease in the QoL

Conclusions & Implications

- Our estimate of utility in SubHypo (0.89) is not very different from values reported previously in non-pregnant women with SubHypo (0.87)¹
- However, it is somehow lower than the expert estimates used in previous economic models (0.9 and 1.0)²
- In the real world, the utility in euthyroid pregnant women is $\neq 1$ (unlike previously used *per definitionem*)
- SubHypo is accompanied by specific symptoms: decreased cognition, eye symptoms, and increased anxiety → implication for targeted screening?
- The symptoms of SubHypo differ from those consensually attributed to hypothyroidism³, notably depression
- Only anxiety impacted overall well-being
- EQ-5D-5L and ThyPRO-39 can be now mapped in similar populations

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Appendix: Detailed overview of the individual ThyPRO-39 symptoms

	Euthyroid	SubHypo	p-value	p-value		Euthyroid	SubHypo	p-value	p-value
	mean ± SD	mean ± SD	value	adjusted*		mean ± SD	mean ± SD	p-value	adjusted*
Sample Size	174	61			Sample Size	174	61		
Fullness in the neck	0.26 ± 0.71	0.43 ± 0.69	0.015	0.106	Afraid or anxious	0.59 ± 0.69	0.90 ± 0.85	0.008	0.015
Pressure in the throat	0.15 ± 0.46	0.18 ± 0.47	0.516	0.476	Felt tense	0.37 ± 0.60	0.82 ± 0.92	<0.001	0.000
Discomfort swallowing	0.11 ± 0.37	0.16 ± 0.42	0.296	0.224	Felt uneasy	0.42 ± 0.64	0.87 ± 0.90	<0.001	0.000
Trembling hands	0.14 ± 0.45	0.23 ± 0.69	0.426	0.448	Felt sad	0.48 ± 0.74	0.79 ± 0.84	0.002	0.010
Tendency to sweat	0.51 ± 0.80	0.57 ± 0.85	0.582	0.925	Felt unhappy	0.26 ± 0.68	0.38 ± 0.76	0.216	0.441
Palpitations	0.36 ± 0.68	0.66 ± 0.77	0.001	0.014	Had self-confidence	1.80 ± 1.00	1.57 ± 0.87	0.075	0.554
Sensitive to cold	0.83 ± 0.98	0.89 ± 1.03	0.750	0.895	Easily felt stressed	0.91 ± 0.94	1.03 ± 0.98	0.382	0.296
Upset stomach	1.08 ± 1.15	1.15 ± 1.25	0.780	0.884	Mood swings	1.07 ± 0.89	1.36 ± 0.93	0.025	0.094
Dryness or grittiness in the yes	0.24 ± .61	0.54 ± 0.77	<0.001	0.001	Felt control of your life	2.66 ± 1.22	2.33 ± 1.17	0.029	0.366
Impaired vision	0.10 ± 0.32	0.21 ± 0.45	0.030	0.026	Difficulty being together with other people	0.18 ± 0.53	0.31 ± 0.56	0.013	0.131
Very sensitive to light	0.16 ± 0.49	0.33 ± 0.63	0.017	0.072	Feel you were a burden to other people	0.16 ± 0.50	0.20 ± 0.44	0.255	0.586
Swollen hands or feet	0.17 ± 0.42	0.21 ± 0.49	0.548	0.208	Had conflicts with other people	0.25 ± 0.61	0.34 ± 0.57	0.113	0.725
Dry skin	0.90 ± 0.91	1.28 ± 1.05	0.012	0.037	Had difficulty managing your daily life	0.33 ± 0.61	0.46 ± 0.83	0.414	0.263
Itchy skin	0.52 ± 0.79	0.69 ± 1.07	0.596	0.514	Not be able to participate in life around you	0.21 ± 0.53	0.30 ± 0.61	0.311	0.435
Been tired	1.88 ± 1.03	2.07 ± 1.12	0.209	0.212	Everything takes longer to do	0.56 ± 0.83	0.54 ± 0.81	0.939	0.995
Difficulty getting motivated to do anything	0.95 ± 0.98	1.43 ± 1.04	0.001	0.003	Disease affected appearance	0.08 ± 0.33	0.20 ± 0.57	0.090	0.088
Felt energetic	1.80 ± 0.93	1.57 ± 0.88	0.065	0.587	Bothered by other people looking at you	0.06 ± 0.26	0.13 ± 0.39	0.092	0.112
Difficulty remembering	0.37 ± 0.62	0.52 ± 0.72	0.114	0.225	Thyroid disease influenced clothes you wear	0.10 ± 0.38	0.13 ± 0.39	0.284	0.740
Unclear thinking	0.32 ± 0.63	0.62 ± 0.78	0.001	0.012	Thyroid disease had a negative effect on QoL	0.20 ± (0.51)	0.30 ± 0.61	0.214	0.289
Difficulty concentrating	0.40 ± 0.65	0.62 ± 0.66	0.006	0.054					

Appendix: Individual EQ-5D-5L domains

	Total	Euthyroid	SubHypo	p-value
Mobility 1	231 (91%)	162 (93%)	52 (85%)	0.074
Mobility 2	21 (8%)	12 (7%)	8 (13%)	0.074
Mobility 3	1 (0%)	0 (0%)	1 (2%)	0.074
Self-care 1	247 (98%)	170 (98%)	60 (98%)	0.759
Self-care 2	6 (2%)	4 (2%)	1 (2%)	0.759
Usual activities 1	204 (81%)	143 (82%)	47 (77%)	0.358
Usual activities 2	42 (17%)	28 (16%)	11 (18%)	0.358
Usual activities 3	7 (3%)	3 (2%)	3 (5%)	0.358
Pain/discomfort 1	180 (71%)	125 (72%)	43 (70%)	0.152
Pain/discomfort 2	64 (25%)	46 (26%)	14 (23%)	0.152
Pain/discomfort 3	9 (4%)	3 (2%)	4 (7%)	0.152
Anxiety/Depression 1	196 (77%)	143 (82%)	38 (62%)	0.006
Anxiety/Depression 2	47 (19%)	25 (14%)	19 (31%)	0.006
Anxiety/Depression 3	10 (4%)	6 (3%)	4 (7%)	0.006