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ABSTRACT

OBJECTIVE: Diabetes increases in hypothyroidism but also in hyperthyroxinemia, which seems contradictory. Both, high free thyroxyne (fT4) and TSH appear in the resistance to thyroid hormone (RTH) syndrome. A mild acquired RTH might occur in the general population and be associated with diabetes. Aim: to analyze the association of RTH indices (the Thyroid Feedback Quantile-based Index [TFQI], proposed in this work, and the previously used Thyrotroph T4 Resistance Index and TSH Index) with diabetes.

METHODS: US representative sample: 5129 individuals≥20 years of age from the 2007-2008 National Health and Nutrition Examination Survey (NHANES). RTH indices: A US-referenced Parametric TFQI (PTFQI) can be calculated with the spreadsheet formula "=NORM.DIST(fT4_cell_in_pmol_per_L,10.075,2.155,TRUE)+NORM.DIST(LN(TSH_cell_in_mIU_per_L),0.4654,0.7744,TRUE)-1". Outcomes: Glycohemoglobin≥6.5%, diabetes medication, diabetes-related deaths (diabetes as contributing cause of death), and, additionally, in a fasting subsample, diabetes and metabolic syndrome. Logistic and Poisson regressions were adjusted for sex, age, and race/ethnicity.

RESULTS: Odd ratios for 4th vs 1st quartile of TFQI were 1.73(1.32,2.27) (p-trend=0.002) for positive glycohemoglobin and 1.66(1.31,2.10) (p-trend=0.001) for medication. Diabetes-related death rate ratio for TFQI>median was 4.81(1.01,22.94) (p-trend=0.015). Further adjustment for body mass index and restriction to normothyroid individuals yielded similar results. Per 1 standard deviation in TFQI, odds increased 1.13(1.02,1.25) for diabetes and 1.16(1.02,1.31) for metabolic syndrome. The other RTH indices showed similar associations for diabetes-related deaths and metabolic syndrome.

CONCLUSION: Higher values in RTH indices are associated with obesity, metabolic syndrome, diabetes, and diabetes-related mortality. RTH may reflect energy balance problems driving type 2 diabetes. These indices may facilitate monitoring treatments focused on energy balance.

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INTRODUCTION

Recent evidence suggests that hyperthyroxinemia may be cross-sectionally and prospectively associated with type 2 diabetes[1]. This is at odds with the physiological metabolism-activating action of thyroid hormones, which is considered capable of ameliorating obesity-related morbidities[2]. It is also in conflict with the increased incidence of diabetes reported among patients with hypothyroidism[3] and with the increased prevalence of metabolic syndrome described in the upper-normal range of the pituitary thyroid-stimulating hormone (TSH, also known as thyrotropin)[4], a range associated with lower thyroid activity. Previous evidence is inconsistent[4], some studies find diabetes or metabolic syndrome associated with TSH, but not with thyroid hormones whereas others find an association only with thyroid hormones, occasionally linking opposite ends of the thyroid hormones concentration range with diabetes. The effect of thyroid hormones on insulin sensitivity differs by tissue, it enhances glucose uptake in the muscle but reduces it in the liver[5]. The overall net effect in hypothyroidism favors insulin resistance but in hyperthyroidism it may also occasionally favor glucose intolerance[5]. These metabolic mechanisms described in clinical thyroid diseases may not be enough to explain the associations found within the normothyroid range.

Physiologically, thyroid hormones and TSH are inversely correlated due to a negative feedback loop. However, high thyroid hormones coexist with high TSH in individuals with Resistance to Thyroid Hormone (RTH) syndrome, an inherited autosomal recessive trait[6–8]. Yet, a possibly reversible acquired resistance to thyroid hormone, due to homeostatic compensation, has been hypothesized[9]. Prolonged fasting produces drops in TSH and increases in pituitary sensitivity to thyroid hormones[10,11]. In contrast, morbidly obese individuals tend to have higher levels of both thyroid hormones and TSH[12]. Resistance to thyroid hormone phenomena can be systematized in central

resistance, which affects the feedback loop set-point in the central nervous system, and peripheral resistance, which decreases hormones metabolic effects. The former are easier to evaluate than the latter because they can be quantified just observing thyroid hormones and TSH concentrations or indices derived from them[13,14], although suppression tests have also been described[15].

Thus, given the thyroid feedback loop, the aforementioned reports showing association of high thyroid hormones and/or high TSH, with the prevalence and incidence of metabolic syndrome and diabetes provide apparently contradicting results. In this paper we hypothesized that these conflicting results might be conciliated if high thyroid hormones and high TSH co-occurrence in diabetes reflected a central resistance to thyroid hormone. If that were the case, this central resistance would probably be the expression of a general reduced sensitivity to thyroid hormones, i.e., not only central but also peripheral. This resistance to thyroid hormone could be one additional characteristic of the cardiometabolic traits predicting diabetes. We analyzed Continuous National Health And Nutrition Examinations Survey (NHANES)[16] data to gain insight into this issue and propose the Thyroid Feedback Quantile-based Index (TFQI), a new resistance to thyroid hormone index focused on deviations close to normality.

METHODS

Design and participants

Thyroid hormones and TSH were measured in serum in 5222 (N_1) adults 20y and older in the Continuous National Health And Nutrition Examinations Survey (NHANES)[16] performed in 2007 and 2008, which recruited a representative sample of the non-institutionalized US population. Data on mortality up to 2011 from the National Death Index is available for all but 6 individuals. The present study estimates cross-sectional associations between resistance to thyroid hormone indices and

diabetes-related conditions as well as longitudinal associations between the indices and the diabetes-related mortality rate. Analyses were performed using the entire NHANES dataset (N_1) and several subsets (main complete-case sample, N_2=5129; normothyroid sample, N_3=4750; and fasting normothyroid sample, N_4=1997) (see flow chart in supplementary materials). NHANES participants provided their written informed consent to participate in the survey, which was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board (Continuation of Protocol #2005-06).

Thyroxine, TSH, and resistance to thyroid hormone indices

Free thyroxine (fT4) was quantified with the Access Free T4 (FRT4) assay, a two-step enzyme immunoassay, and TSH was quantified with the Access HYPERsensitive human thyroid-stimulating hormone (hTSH) assay, a two-site immunoenzymatic ("sandwich") assay. Measurements were performed at the University of Washington (Seattle, WA). The laboratory normality reference ranges were 7.74-20.64 pmol/L for fT4 and 0.34-5.60 mIU/L for TSH.

Thyrotroph T4 Resistance Index (TT4RI) was calculated as $\mathbf{fT4(pmol/L) \cdot TSH(mIU/L)}$ [13]. TSH index (TSHI) was calculated as $\mathbf{\ln TSH(mIU/L) + 0.1345 \cdot fT4(pmol/L)}$ [14].

Thyroid Feedback Quantile-based Index (TFQI), a new resistance to thyroid hormone index

Given encouraging preliminary results from studying participants who were simultaneously in the extreme quartiles of fT4 and TSH (see statistical analyses and results sections), we developed a new index to quantify, in a continuous manner, deviations from the median pituitary response (inhibition) to thyroid hormones, the TFQI.

Ranks (order position from minimum to maximum value) of fT4 and TSH were converted to quantiles between 0 and 1, taking into account sampling weights. Fractional quantiles are a generalization that

summarizes in a single fraction the sequential number of part and the number of parts, e.g. the upper limit of the second tertile is the value of the quantile 0.66 and the upper limit of the third quartile is the value of the quantile 0.75. That conversion is achieved by applying the population empirical cumulative distribution function (cdf) to hormones concentration. TFQI was calculated as **cdf fT4-(1-cdf TSH)**, i.e., the difference between fT4 quantile and the reversed TSH quantile, because they are inversely correlated in the negative feedback loop. This index ranges between -1 and 1. Negative values indicate lower TSH (higher inhibition by fT4) than that expected for the actual fT4 (which means higher sensitivity to fT4). Similarly, positive values indicate higher TSH (lower inhibition by fT4) than that expected for the actual fT4 (lower sensitivity to fT4). Median TSH response to fT4 is represented by the value 0. This index is more stable than TT4RI and TSHI at abnormal ranges of the thyroid-gland responsiveness to TSH. That is, TFQI does not reach extreme values in individuals with thyroid-gland-caused (primary) clinical hyper- or hypothyroidism (see datapoints in the top-left and bottom-right areas of TSH vs fT4 scatterplots in Figure S1).

In order to provide an index that can be calculated for any new value or adapted to other populations, an approximation with the same range and interpretation, the Parametric Thyroid Feedback Quantile-based Index (PTFQI) can be obtained from fT4 in pmol/L and TSH in mIU/L using the standard normal cumulative distribution function as **$\Phi((fT4-\mu_{fT4})/\sigma_{fT4})-(1-\Phi((\ln TSH-\mu_{\ln TSH})/\sigma_{\ln TSH}))$**, where μ_{fT4}=10.075, σ_{fT4}=2.155, $\mu_{\ln TSH}$=0.4654, and $\sigma_{\ln TSH}$=0.7744 for the US population. This can be easily achieved with the Excel or LibreOffice spreadsheet formula **=NORM.DIST(*fT4_cell*,10.075,2.155,TRUE)+NORM.DIST(LN(*TSH_cell*),0.4654, 0.7744,TRUE)-1**.

Other variables

Demographic (including race/ethnicity as non-hispanic white, non-hispanic black, and other), clinical interview, physical examination, and other laboratory variables were obtained following protocols available in NHANES operation manuals[16]. Briefly, glucose was measured with the glucose oxidase method and glycohemoglobin (HbA1c) on the A1c G7 HPLC Glycohemoglobin Analyzer (Tosoh Medics, Inc., San Francisco, Ca, US). Blood was drawn from participants who were visited at any time throughout the day, except for a subsample of participants appointed for a morning visit and requested to fast. In the main sample dataset (which includes non-fasting data), high HbA1c (≥6.5%, i.e., ≥48 mmol/mol) and use of diabetes medication were analyzed, as they can be interpreted as proxies for diabetes. In the fasting subsample, diabetes was defined as fasting (≥8h) glycemia ≥126 mg/dL, or presenting the previously mentioned proxies. Obesity was defined as a body mass index (BMI) ≥30 kg/m^2. Metabolic syndrome diagnosis was established using the harmonized criteria[17], i.e., diagnosis was issued when meeting three of the following criteria: a) Waist circumference ≥102 cm in men or ≥88 cm in women; b) triglycerides ≥150 mg/dL; c) HDLc <40 mg/dL in men or <50 mg/dL in women; d) systolic or diastolic blood pressure ≥130 mmHg or ≥85 mmHg, respectively (or receiving medication for hypertension); and e) glucose ≥100 mg/dL (or receiving medication for diabetes).

Mortality

Survey data were linked with the National Death Index by the National Center for Health Statistics (NCHS). Besides the leading cause of death, records also include contributing causes of death in a 20 entity-axis multiple causes of death codes. The public-use linked mortality dataset provided by the NCHS includes a flag variable for diabetes when ICD-10 codes E10-E14 appear as one of the 20 contributing or multiple causes of death. We used this flag, i.e., diabetes-related death, as our endpoint.

Statistical analyses

Mean and standard deviation of thyroid parameters were calculated for population sex, age, and race strata. TSH and TT4RI were processed in the logarithmic scale given their skewed distributions. We created scatterplots of TSH vs fT4 and plotted population-based percentiles of the indices.

The interesting results observed when we compared participants who were either at the lowest or at the highest quartiles of fT4 and TSH simultaneously (see supplementary material and results section) led us to develop TFQI and PTFQI (described above). These indices enabled us to study pituitary feedback response with a continuous variable.

We created population-based quartiles for each resistance to thyroid hormone index (TFQI, PTFQI, TT4RI, and TSHI). Differences, odds ratios (OR), and rate ratios (RR) across quartiles, using the lowest as reference were estimated with generalized linear, logistic, and Poisson regression models respectively. Model 1 adjusted for sex, age, and race. Model 2 further adjusted for BMI. Model 3 further adjusted for initially presenting HbA1c≥6.5% and diabetes medication use. For each trend, significance was tested with each index quartile ordinal as a continuous variable. Given that there were no diabetes-related deaths within the first quartile of 3 indices, this outcome was compared between values above and below the median, and trend was tested with each index as a continuous variable.

In the main sample and the normothyroid sample, interquartile comparisons were performed for BMI, obesity, HbA1c≥6.5%, diabetes medication use, and diabetes-related mortality. BMI was modeled with linear regression; obesity, HbA1c≥6.5%, and diabetes medication were modeled with logistic regression, and death was modeled with Poisson regression.

In the fasting subsample, OR for diabetes, metabolic syndrome, and metabolic syndrome criteria were calculated for one standard deviation increase of resistance to thyroid hormone indices except for

TT4RI. This index was analyzed using the logarithmic scale and its OR was calculated for a TT4RI multiplicative increase by a standard deviation equivalent (x $2^{sd\ log2\ TT4RI}$). Diabetes, metabolic syndrome, and metabolic syndrome criteria were modeled with logistic regression.

As part of sensitivity analyses we further adjusted models for education level, physical activity performed at work or during leisure time, and daily sedentary time. All analyses were performed with statistical computing software R[18] version 3.4.4 with the package "survey"[19] to account for the NHANES complex survey design.

RESULTS

The 5222 participants in the sample represented the US population 20y and older and they had a mean (sd) age of 46.9y (16.6) (Table 1). Indices of resistance to thyroid hormone were higher among older people and lower among black individuals (Table 1).

In a preliminary analysis, obesity prevalence and, especially, HbA1c≥6.5% and use of diabetes medication showed a tendency to be higher among participants whose fT4 and TSH were simultaneously above their 75th percentiles (Supplementary material: Preliminary analysis).

A scatterplot of TSH vs fT4 shows the negative correlation of these variables while the contour lines show selected percentiles for each one of the resistance to thyroid hormone indices (Figure 1 and Figure S1). TT4RI and TSHI (Figure S1) take extreme values (>95th and <5th percentile) for almost all patients diagnosed with clinical hypo- and hyperthyroidism. This seemingly inappropriate result together with our observation that a quantile-based approach (Supplementary material: Preliminary analysis) uncovered the above mentioned associations and provided more moderate values among patients with clinical thyroid-gland-caused (primary) disease is what led us to develop TFQI.

BMI, obesity prevalence, HbA1c≥6.5%, and use of diabetes medication were progressively higher across TFQI quartiles after adjusting for sex, age, and race (all p<0.01). Odds ratios of the 4th vs the 1st TFQI quartile for HbA1c≥6.5% and use of diabetes medication were 1.73 (95%CI 1.32,2.27) and 1.66 (1.31,2.10) respectively and the association was independent of BMI, given that after adjustment, ORs estimations were only partially reduced to 1.43 (1.07,1.92) and 1.39 (1.10,1.75) respectively (p for trend<0.05) (Table 2). Participants had a median follow-up of 3 years and 11 months, during which there were 27 deaths with diabetes listed within the entity-axis multiple cause of death. In 9 of these cases diabetes was the leading cause of death. For participants with TFQI above the median (vs below it), sex-, age-, and race-adjusted rate ratio (RR) for diabetes-related death was 4.81 (1.01,22.94). TFQI was linearly associated with the rate for diabetes-related death (p=0.015), and the association remained statistically significant even after adjustment for BMI (p=0.035). One fourth of deaths occurred among participants without initial diabetes-proxies presence. However, in spite of a similar magnitude of association for being above the median: RR 3.51 (0.78,15.85), such a small number of events made it impossible to detect a statistically significant association after adjustment for the initial condition. All results were similar when examining PTFQI instead of TFQI (Supplementary material: Table Main sample - PTFQI). Adjusting for education, physical activity, and sedentary time did not substantially change these results (Supplementary material: Sensitivity analysis).

TT4RI and TSHI were cross-sectionally associated with obesity, although not with diabetes proxies. Nonetheless, both were prospectively associated with diabetes-related mortality independently of initial diabetes-proxies presence (Supplementary material: Tables Main sample - TT4RI and Main sample - TSHI). All these results persisted in the normothyroid subsample (Supplementary material: Tables Normothyroid sample) with the exception of RR for mortality. Although the magnitudes for its indicators were very similar, they failed to reach statistical significance probably due to the statistical

loss of power caused by excluding 2 deceased participants who had marginally subclinical hypothyroidism (Figure 1 and Supplementary material: Tables Normothyroid sample).

We tested cross-sectional associations of the indices with diabetes and metabolic syndrome in the fasting subsample of normothyroid participants. Only TFQI (and its approximation PTFQI) was associated with diabetes based on glycemia, HbA1c, and medication. All resistance to thyroid hormone indices were associated with metabolic syndrome in general and with HDL and blood pressure metabolic syndrome criteria. Lastly, TT4RI and TSHI were also associated with triglycerides criterion (Table 3).

DISCUSSION

Based on a sample representative of the US population we provide evidence of the association between indices measuring resistance to thyroid hormone and prevalence of obesity, diabetes, and metabolic syndrome as well as between these indices and the incidence of diabetes-related deaths. These associations were also identified within the normal thyroxine and TSH ranges. Not only these results reconcile previous reports linking diabetes to hypothyroidism[3] and to hyperthyroxinemia[1] but they also call for a new interpretation of thyroid hormones changes associated with diabetes.

As far as we are aware of, this is the first time that indices of resistance to thyroid hormone have been evaluated in the general population and associated with cardiometabolic health characteristics. Our analyses showed that TT4RI and TSHI indices seemed to systematically classify thyroid-gland-caused (primary) hypothyroidism and hyperthyroidism (clinical and subclinical) as resistant or very sensitive to thyroid hormones, respectively. Thus, we proposed a new index, thyroid feedback quantile-based index (TFQI). TFQI is based on the empirical joint distribution of fT4 and TSH with the advantage of not yielding extreme values in cases of thyroid gland dysfunction. Its parametric version (PTFQI) can

readily be used as a formula to calculate the index for any particular individual with reference to the US population, or it can be adapted to other reference populations.

All these resistance to thyroid hormone indices measure central sensitivity/resistance, i.e., the grade of pituitary gland inhibition by fT4 levels. Thus, they evaluate the set-point of the central regulation of thyroid hormones concentration. Among participants with high values, peripheral resistance could also be present because, despite higher fT4, we find in this group higher prevalence of obesity, diabetes, and metabolic syndrome, phenotypes usually associated with hypothyroidism.

Thyroid hormones increase energy expenditure and thermogenesis[20], increase glucose and fatty acid oxidation in muscle[21] and the liver[22], increase adipose tissue lipolysis[23], and promote lower body weight[24]. In sum, an overall effect on metabolism that would prevent diabetes development. Interestingly, thyroid hormones also sensitize to catecholamines, which increase liver hepatic glycogenolysis, neoglucogenesis, and glucose output[25], reduce insulin anabolic actions in the liver, and increase glucose intestinal absortion[5]. Though the latter effect plays a minor role in glucose levels derangement. In overt hyperthyroidism, these changes could be responsible for decompensation of preexisting diabetes and even trigger ketoacidosis[25], but they may be less important within the normal range of thyroid hormones and unlikely to cause diabetes onset in a previously metabolically normal individual.

Besides secretion regulation by the hypothalamic-pituitary-thyroid axis, thyroid hormones action is modulated[6,26] at cell membrane transport, enzymatic modification into active and inactive species by deiodinases, and nuclear receptors. Nutritional signals can modulate the thyroid system during some of the regulation, secretion, and action steps. Hypothalamic neurons inhibit secretion when leptin levels fall, providing a system to protect against starvation[27]. Meanwhile, an increase in leptin derived from adipose tissue accumulation may indicate availability of energetic substrates, and thus, the subsequent

activation of the thyroid axis could also be interpreted as a homeostatic regulation. Accordingly, high TSH -within normal levels- is associated with increased adiposity[28] and consistent with near-hypothyroidism hormonal end-effects. This can be interpreted as a deficient thyroid hormone production in relative terms, unable to meet the metabolic increase required to compensate fat accumulation. Interestingly, in morbidly obese individuals thyroid hormones are also elevated[12] hinting to a downstream signal problem. Activity of deiodinases[29], epigenetic modification of histones, and interaction with signaling of other transcription factors[30] also regulate, at the cellular level, thyroid hormones actions on metabolism. In addition, in obesity a steady consumption of high-calorie foods may even overpower the thyroid stimulus that increases resting metabolic rate[31], leading to a biochemical phenotype compatible with an apparent resistance to thyroid hormone. We have previously proposed a similar interpretation for the origin of insulin resistance in obesity[32].

From a clinical point of view, there seems to be a gradient of increasing thyroid hormones levels -within the normal range- across early stages of diabetes[33]. Furthermore, prospectively, higher levels of thyroid hormones are associated with incident diabetes[1] in spite of the fact that hypothyroidism is the disorder that clearly increases diabetes risk[3]. As resistance to thyroid hormone is one of the differential diagnoses when both fT4 and TSH are elevated[34], our results offer an explanation for thyroid profiles commonly found in the diabetic patient. That is, at the population level, measurements of resistance to thyroid hormone are cross-sectionally associated with diabetes, independently of the degree of obesity as measured with BMI, suggesting that there might be other undelying mechanisms linking diabetes and resistance to thyroid hormone. Furthermore, prospectively, these measurements were also associated with diabetes-related deaths, even independently of the initial diabetic status.

Measurements of resistance to thyroid hormone were also cross-sectionally associated with metabolic syndrome on a consistent basis. Previous attempts to relate metabolic syndrome with the thyroid axis

either showed an association with TSH but not with fT4[35] or yielded inconsistent results. We hypothesized that whereas a metabolic status with excess energy may stimulate the thyroid axis, the thyroid boost to energy expenditure fails to compensate. This results in an expression compatible with resistance to thyroid hormone. Thyroid stimuli still increase, although insufficiently, the uncoupled thermogenic oxidative processes, which can be observed as an increase of oxidative stress in metabolic syndrome[36]. A sustained compensatory TSH stimulus could also explain, in part, the recently reported association of metabolic syndrome, insulin resistance, and diabetes with thyroid enlargement, thyroid nodules, and thyroid cancer[37]. We can not exclude that other conditions, like immunity disorders, could also explain a coincidence of elevated thyroid hormones, due to autoimmune thyroid disease, and Latent Autoimmune Diabetes of Adults (LADA). However, from a population perspective, energy imbalance is much more prevalent.

Type 2 diabetes requires a broad clinical management beyond glucose control, focused on energy balance. Monitoring resistance to thyroid hormone could be used to evaluate the intended reversal of the abnormal energetic balance. Interestingly, where traditional interventions of food intake reduction and physical exercise increase seem to fail, new treatments trying to modify the activity of uncoupling proteins have been proposed [2,38,39] .

This study is based on a representative sample of the US population with strict data collection protocols. Consistency in results between cross-sectional associations and longitudinal mortality analyses support our conclusions. However some limitations exist. Indices of resistance to thyroid hormone increase markedly with aging. Whereas all analyses are adjusted for age and other potential confounders, some residual confounding may remain. Given that many factors may be associated with diabetes and metabolic syndrome, it is not possible to adjust for unavailable variables and unknown factors, and the potential residual confounding must be considered when interpreting the study results.

One anti-diabetic oral agent, metformin, lowers TSH (leaving fT4 unchanged) among patients with hypothyroidism[37] and there is some evidence hinting that it sensitizes the pituitary gland and peripheral tissues to thyroid hormones action[40]. Thus, our results may underestimate the true association between resistance to thyroid hormone and diabetes, i.e., the association may be even stronger than the statistically significant association reported here. Because our analysis focused on resistance to thyroid hormone indices, which are all fT4-based, fT3 was intentionally excluded from the models since it was considered to be downstream in the action pathway. Actually, deiodinases balance may play a role in the modulation of sensitivity to thyroid hormones[29] and future projects should be devoted to specifically study their role in resistance to thyroid hormone in obesity, metabolic syndrome, and diabetes. Diabetes and related outcomes were based on one single measurement of HbA1c or fasting plasma glucose, which is a common limitation in population-based studies. Finally, the small number of observed diabetes-related deaths limits the statistical power needed to find subtle effects as well as to perform subgroup analyses. Notwithstanding, the association was strong enough to bear statistically significant results.

CONCLUSIONS

Higher values in indices of resistance to thyroid hormone are associated with obesity, metabolic syndrome, and diabetes for the entire population in general, and also for normothyroid individuals, in particular. Higher values are also prospectively associated with diabetes-related mortality. These associations with diabetes morbidity and mortality were independent of obesity. We propose the new thyroid feedback quantile-based index (TFQI) to identify mild levels of acquired resistance in the general population. Type 2 diabetes is in part driven by an energy balance problem and the associated central resistance measured by indices of resistance to thyroid hormone may be the result of the

physiologic contra-regulation against it. These indices may facilitate the monitoring and evaluation of new therapies that focus on energy expenditure.

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The corresponding author had full access to all the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis, and had final responsibility for the decision to submit for publication.

Authors' contributions: ML conceptualized the research question and designed the study. ML and BM-F performed the statistical data analysis. ML, BM-F, JML-B, and FM interpreted the results and ML and BM-F wrote the manuscript. RM-G, JAC, PG-C, AC, and FM revised the manuscript for important intellectual content. All authors approved the final version of the manuscript for publication.

The authors have no conflicts of interest regarding this work.

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Table 1. Characteristics and thyroid parameters of the US population represented in the NHANES sample (N_1=5222).

N_1=5222	%	fT4	p	TSH*	p	TFQI	p	TT4RI*	p	TSHI	p
All		10.08		1.59		0.00		15.73		1.82	
		(2.15)				(0.37)				(0.74)	
Male	48.3	10.04	0.431	1.62	0.220	0.00	0.403	16.02	0.147	1.83	0.299
Female	51.7	10.11		1.57		-0.01		15.47		1.81	
[20y,40y)	37.0	10.00	<0.001	1.47	<0.001	-0.05	<0.001	14.41	<0.001	1.73	<0.001
[40y,60y)	39.3	9.80		1.64		-0.03		15.79		1.81	
[60y,oldest]	23.7	10.67		1.72		0.13		17.96		1.98	
White	70.7	10.06	0.234	1.69	<0.001	0.02	<0.001	16.68	<0.001	1.88	<0.001
Black	10.0	9.91		1.19		-0.17		11.51		1.51	
Other	19.3	10.22		1.49		-0.01		14.95		1.77	

Percentages, mean (standard deviation) of parameters. * were calculated as geometric means. P values are for differences between groups and were calculated from linear regression models.
N, number of participants; y, years; fT4, free Thyroxyne; TSH, Thyroid-Stimulating Hormone; TFQI, Thyroid Feedback Quantile-based Index; TT4RI, Thyrotroph T4 Resistance Index; TSHI, TSH Index.

Table 2. Association of thyroid feedback quantile-based index (TFQI) with BMI, obesity, high HbA1c, use of diabetes medication, and diabetes-related deaths in the main sample (N_2=5129).

	TFQI				
	Q1	**Q2**	**Q3**	**Q4**	
	[-1,-0.25)	**[-0.25,0)**	**[0,0.25)**	**[0.25,1]**	**P-trend**
N (N_2=5129)	1319	1259	1270	1281	
BMI (kg/m2)	**28.1**	**28.0**	**29.0**	**28.8**	
Model 1 (dif.)	0.0	0.1	1.1	0.9	0.006
	(Reference)	(-0.6,0.7)	(0.7,1.5)	(0.1,1.6)	
Obesity(%)	**31.0**	**29.0**	**36.7**	**35.8**	
Model 1 (OR)	1.00	0.93	1.34	1.29	0.001
	(Reference)	(0.76,1.14)	(1.17,1.54)	(1.11,1.50)	
HbA1c≥6.5%(%)	**5.0**	**6.4**	**8.9**	**10.0**	
Model 1 (OR)	1.00	1.28	1.70	1.73	0.002
	(Reference)	(0.96,1.71)	(1.37,2.12)	(1.32,2.27)	
Model 2 (OR)	1.00	1.19	1.38	1.43	0.034
	(Reference)	(0.91,1.54)	(1.06,1.78)	(1.07,1.92)	
Diabetes Medication(%)	**4.8**	**7.2**	**9.2**	**9.9**	
Model1 (OR)	1.00	1.46	1.72	1.66	0.001
	(Reference)	(1.00,2.13)	(1.21,2.44)	(1.31,2.10)	
Model2 (OR)	1.00	1.36	1.41	1.39	0.028
	(Reference)	(0.96,1.94)	(1.00,1.98)	(1.10,1.75)	
Diabetes-related deaths (n)	**0**	**4**	**7**	**16**	
Crude rate (per 100000 person-years)	**0.0**	**38.9**	**108.9**	**211.3**	
Crude rate (per 100000 person-years)	**19.5**		**159.2**		
Model 1 (RR)	1.00		4.81		0.015[#]
	(Reference)		(1.01,22.94)		
Model 2 (RR)	1.00		3.92		0.035[#]
	(Reference)		(0.88,17.51)		
Model 3 (RR)	1.00		3.51		0.099[#]
	(Reference)		(0.78,15.85)		

(see footnote on next page)

Differences, odds ratios (OR), and rate ratios (RR) are estimated with generalized linear, logistic, and Poisson regression models respectively. Model 1 is adjusted for sex, age, and race. Model 2 is further adjusted for BMI. Model 3 is further adjusted for initially presenting HbA1c≥6.5% and using diabetes medication. P-trend is calculated with the TFQI quartile ordinal as a continuous variable except in the models with only 2 categories[#] in which it is calculated with TFQI as a continuous variable.
N, n, number of participants; dif., difference; OR, Odds Ratio; RR, Rate Ratio; 95% Confidence intervals provided within parentheses; BMI, Body Mass Index; HbA1c, glycohemoglobin; TFQI, Thyroid Feedback Quantile-based Index; Q1-Q4, Quartile 1-4.

Table 3. Odds ratios of diabetes, metabolic syndrome, and metabolic syndrome criteria for one standard deviation increase of TFQI, PTFQI, and TSHI, or multiplication by a standard deviation equivalent of TT4RI in the fasting normothyroid sample (N_4=1997)

OR (95% CI) N_4=1997	TFQI (+1sd)	PTFQI (+1sd)	TT4RI (x $2^{sd\ log2\ TT4RI}$)	TSHI (+1sd)
Diabetes	**1.13**	**1.13**	**1.09**	**1.10**
	(1.02,1.25)	**(1.02,1.25)**	**(0.89,1.33)**	**(0.93,1.31)**
p	0.041	0.036	0.420	0.299
Metabolic syndrome	**1.16**	**1.16**	**1.30**	**1.28**
	(1.02,1.31)	**(1.03,1.31)**	**(1.09,1.56)**	**(1.09,1.50)**
p	0.040	0.031	0.014	0.013
Waist criterion	**0.99**	**0.99**	**1.06**	**1.05**
	(0.88,1.11)	**(0.89,1.11)**	**(0.91,1.24)**	**(0.91,1.21)**
p	0.814	0.870	0.439	0.536
Triglycerides criterion	**1.07**	**1.07**	**1.40**	**1.33**
	(0.88,1.30)	**(0.88,1.29)**	**(1.16,1.69)**	**(1.10,1.61)**
p	0.510	0.506	0.005	0.013
HDL criterion	**1.21**	**1.21**	**1.21**	**1.22**
	(1.05,1.39)	**(1.06,1.38)**	**(1.04,1.40)**	**(1.06,1.41)**
p	0.024	0.018	0.034	0.021
Blood pressure criterion	**1.18**	**1.19**	**1.22**	**1.21**
	(1.04,1.34)	**(1.06,1.35)**	**(1.07,1.38)**	**(1.08,1.37)**
p	0.023	0.016	0.013	0.008
Glycemia criterion	**1.06**	**1.06**	**1.08**	**1.07**
	(0.94,1.20)	**(0.94,1.19)**	**(0.88,1.32)**	**(0.90,1.28)**
p	0.364	0.371	0.472	0.461

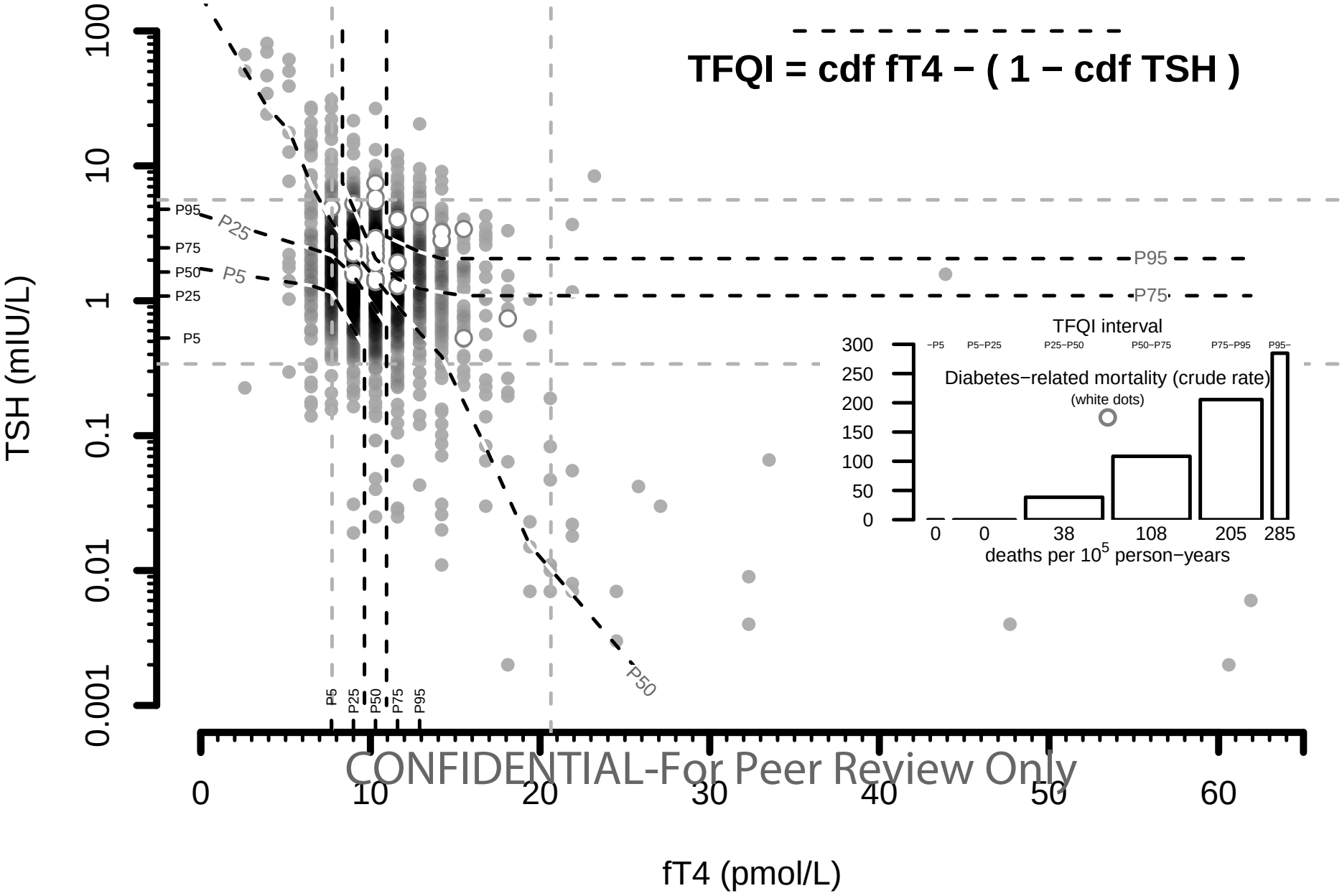
Odds ratios (OR) are estimated with generalized logistic regression models adjusted for sex, age, and race (Model 1) for the increase of 0.37 units TFQI, 0.33 units PTFQI, 0.74 units TSHI (1 standard deviation - sd), and for the multiplication of TT4RI by 2.1 (1 sd equivalent). Indices enter the models as continuous variables. TT4RI enter the model as base 2 logarithm thus OR is for each duplication of its value. ORs are comparable across columns in terms of influence of the index variation on the outcome prevalences.

N, number of participants; OR, Odds Ratio; CI, 95% Confidence intervals, provided within parentheses; HDL, High Density Lipoprotein cholesterol; TFQI, Thyroid Feedback Quantile-based Index; PTFQI, Parametric Thyroid Feedback Quantile-based Index; TT4RI, Thyrotroph T4 Resistance Index; TSHI, TSH Index; sd, standard deviation.

Figure 1

CAPTION
Scatterplot of thyrotropin (TSH) vs free thyroxine (fT4) and Barplot of crude diabetes-related death rates across intervals of thyroid feedback quantile-based index (TFQI) in the NHANES sample (N_1=5222).

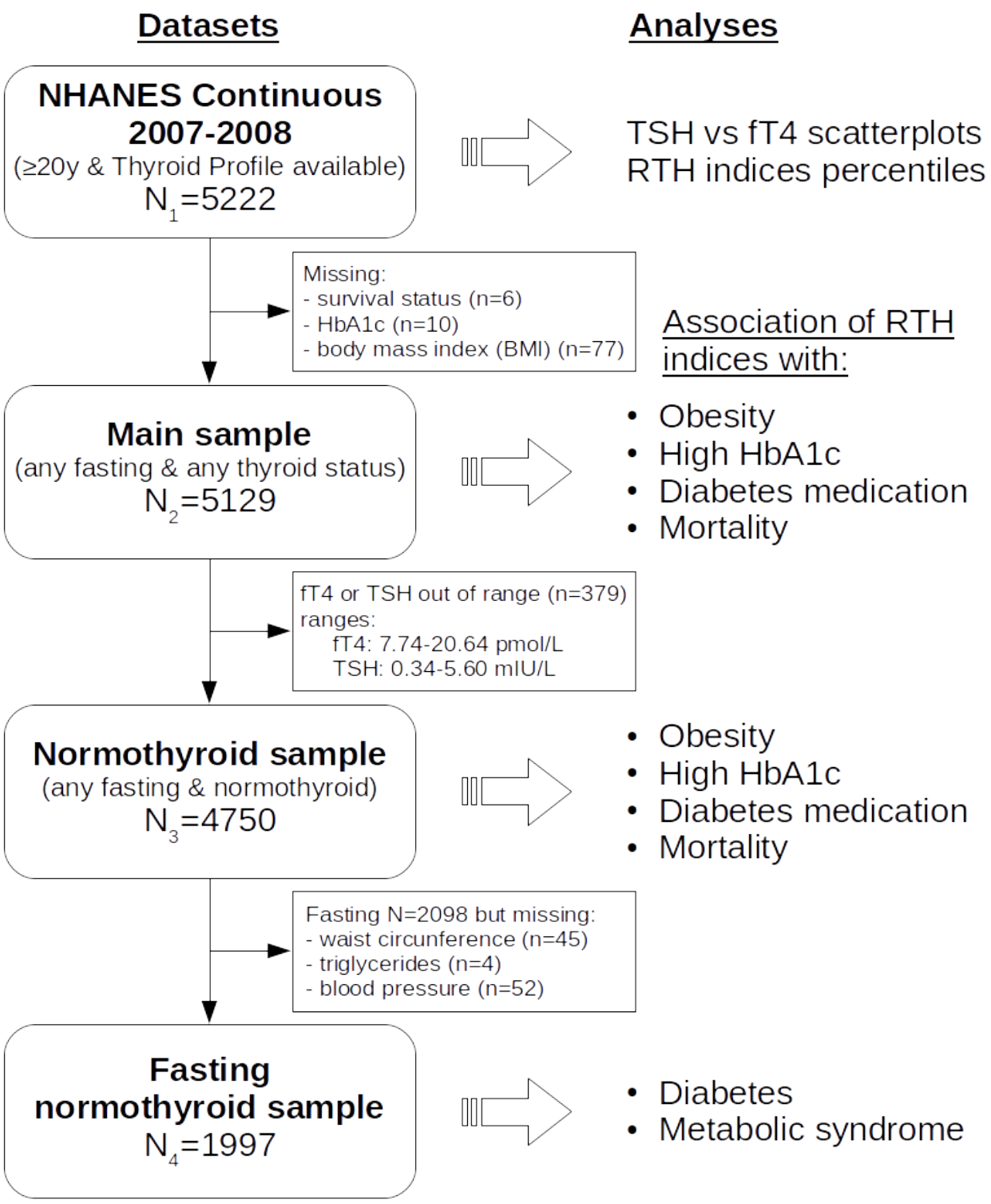
LEGEND
Scatterplot: Dots represent observations. White dots represent participants who died during follow-up and whose deaths were diabetes-related. Grey dashed vertical and horizontal straight lines mark fT4 and TSH normality ranges. Inner marks in the axes represent the 5th, 25th, 50th, 75th, and 95th percentiles of fT4 and TSH. TFQI was calculated for each observation and its value grows gradually across the plot area, from the lower left corner to the upper right corner: Black dashed curves represent the 5th, 25th, 50th, 75th, and 95th percentiles of TFQI. Inner plot: The bars and the number at the base show crude death rates for each TFQI interval (-P_5, P_5-P_{25}, P_{25}-P_{50}, P_{50}-P_{75}, P_{75}-P_{95}, P_{95}-) in deaths per 10^5 person-years. The widths of the bars are proportional to the fraction of the population at risk in each bar so that the area of the bar is proportional to the absolute number of deaths (i.e., the count of white dots in the scatterplot).
N, number of participants; fT4, free Thyroxyne; TSH, Thyroid-Stimulating Hormone; TFQI, Thyroid Feedback Quantile-based Index; cdf, empirical cumulative distribution function; P5, P25, P50, P75, P95, Percentile 5-95.



Supplementary material

Laclaustra M, Moreno-Franco B, Lou-Bonafonte JM, Mateo-Gallego R, Casasnovas JA, Guallar-Castillon P, Cenarro A, Civeira F. Impaired sensitivity to thyroid hormones is associated with diabetes and metabolic syndrome. Diabetes Care. Supplementary material

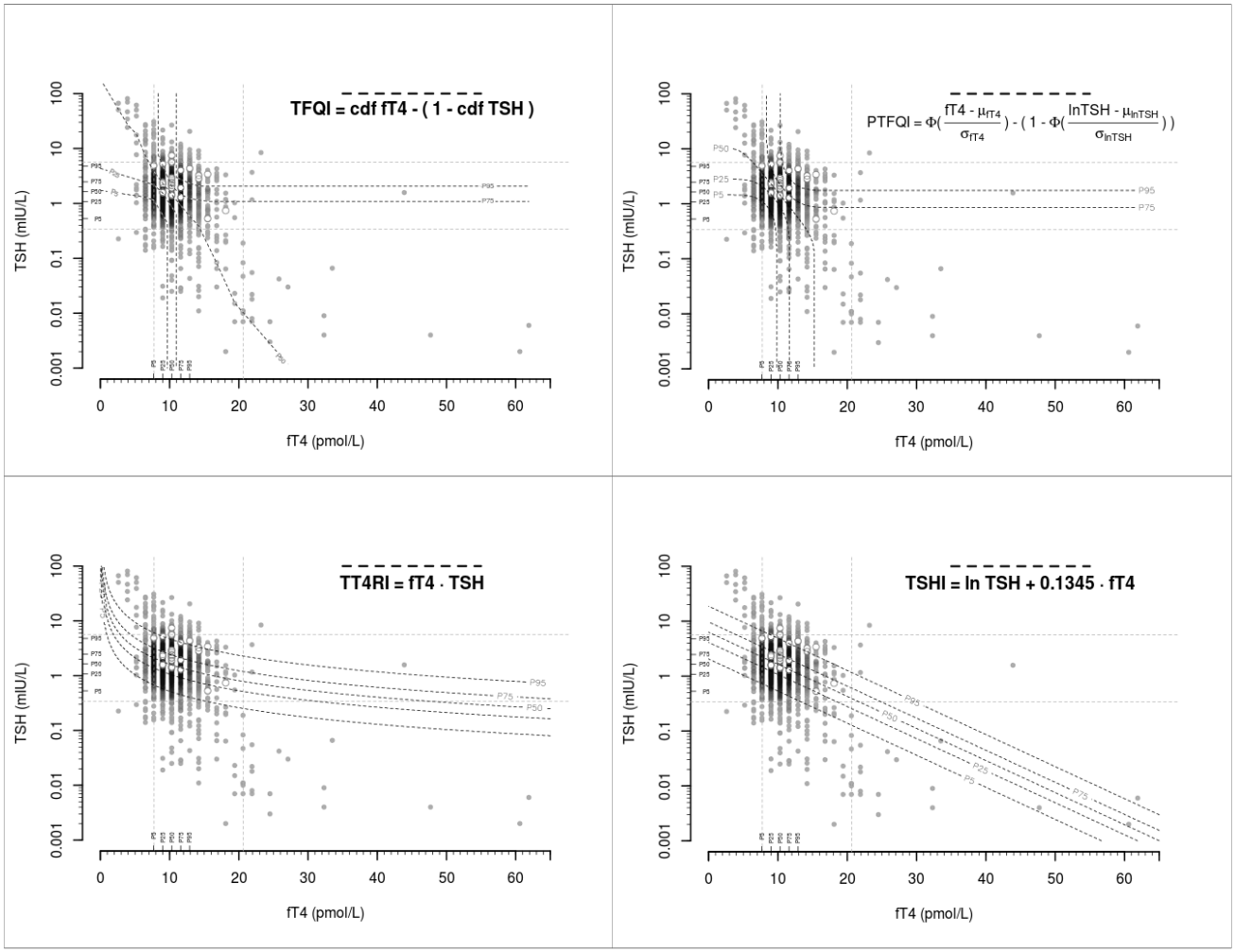
Supplementary material: Flow chart



Thyroid hormones and TSH were measured in serum in 5222 (N_1) adults 20y and older in the Continuous National Health And Nutrition Examinations Survey (NHANES) performed in 2007 and 2008. Data on mortality up to 2011 from the National Death Index is available for all but 6 of them. This NHANES dataset (N_1) was used for description of resistance to thyroid hormone indices and calculation of their population percentiles. A complete-case subset excluding participants with missing data in the variables of interest (main sample, N_2=5129) was used to analyze resistance to thyroid hormone indices cross-sectional association with glycohemoglobin>=6.5% (HbA1c), diabetes medication use, body mass index (BMI), and obesity, and longitudinal estimation of diabetes-related mortality rate. A subsequent subset of normothyroid subjects (Normothyroid sample, N_3=4750), i.e. who have thyroxine and TSH within their normal range (see limits in methods section), was used to confirm that the results were not dependent on overt thyroid illnesses. Finally, a fasting subset of the former normothyroid participants (Fasting normothyroid sample, N_4=1997), also excluding participants with missing data in the variables of interest, was used to analyze resistance to thyroid hormone indices cross-sectional association with glycemia-based diabetes and metabolic syndrome.

Supplementary material: Figure S1

Figure S1. Scatterplots of thyrotropin (TSH) vs free thyroxine (fT4) and percentiles of resistance to thyroid hormone indices in the NHANES sample (N_1=5222)

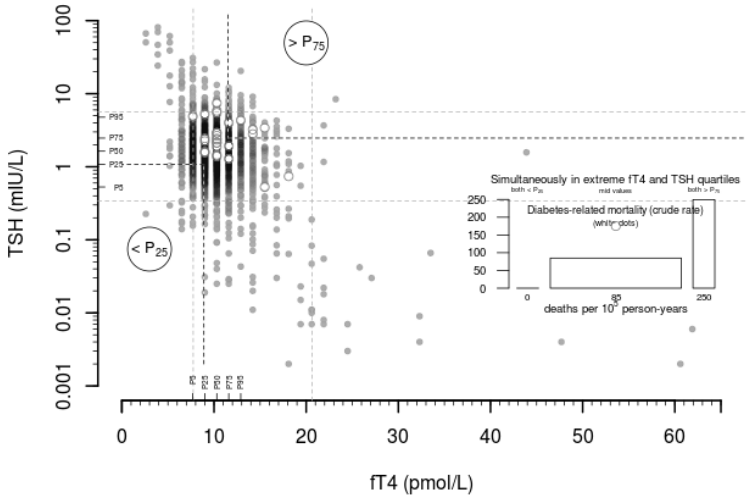


Dots represent observations. Grey dashed vertical and horizontal straight lines mark fT4 and TSH normality ranges. Inner marks in the axes represent the 5th, 25th, 50th, 75th, and 95th percentiles of fT4 and TSH. Black dashed curves represent the 5th, 25th, 50th, 75th, and 95th percentiles of the indices. White dots represent participants that suffered a diabetes-related death during follow-up.
N, number of participants; fT4, free Thyroxyne; TSH, Thyroid-Stimulating Hormone; TFQI, Thyroid Feedback Quantile-based Index; PTFQI, Parametric Thyroid Feedback Quantile-based Index; TT4RI, Thyrotroph T4 Resistance Index; TSHI, TSH Index; cdf, empirical cumulative distribution function; P5, P25, P50, P75, P95, Percentile 5-95.

Note: TT4RI and TSHI take values above their 95th percentile (suggesting resistance to thyroid hormones) for almost all clinical hypothyroidism patients (area beyond the upper-left corner of normality reference lines) and below their 5th percentile (suggesting high sensitivity to thyroid hormones) for almost all clinical hyperthyroidism patients (area beyond the lower-right corner of normality reference lines). In view of that probable inappropriateness of TT4RI and TSHI in primary thyroid diseases, it was pertinent to compare participants with both fT4 and TSH simultaneously high or low avoiding the influence of those clinical patients, which we achieved with a preliminary approach using extreme quartiles (Supplementary material: Preliminary analysis) and a subsequent study using the index TFQI, developed to that end. In contrast with the previous indices, TFQI takes values within the central 50% (between its 25th and 75th percentile) for patients with clinical thyroid-gland-caused (primary) disease.

Supplementary material: Preliminary analysis comparing participants simultaneously in the extreme quartiles of fT4 and TSH

Figure Preliminary analysis. Scatterplot of thyrotropin (TSH) vs free thyroxine (fT4) in the NHANES sample (N_1=5222)



Scatterplot: Dots represent observations. White dots represent participants that suffered a diabetes-related death during follow-up. Grey dashed vertical and horizontal straight lines mark fT4 and TSH normality ranges. Inner marks in the axes represent the 5th, 25th, 50th, 75th, and 95th percentiles of fT4 and TSH. Black dashed angles delimit simultaneous extreme values of fT4 and TSH. Inner plot: The bars and the number at the base show crude death rates for each group.

Table Preliminary analysis. Association of simultaneous extreme fT4 and TSH values with obesity, high HbA1c, and use of diabetes medication in the main sample (N_2=5129).

	fT4 and TSH			
	Both <P_{25}	**Mid values**	**Both >P_{75}**	**P trend**
N (N_2=5129)	152	4662	315	
Obesity(%)	**27.3**	**33.0**	**37.9**	
Unadjusted (OR)	1.00	1.31	1.62	0.070
	(Reference)	(0.82,2.11)	(0.95,2.78)	
Model 1 (OR)	1.00	1.38	1.71	0.064
	(Reference)	(0.87,2.21)	(1.01,2.89)	
HbA1c>=6.5(%)	**4.0**	**7.4**	**12.0**	
Unadjusted (OR)	1.00	1.93	3.28	0.003
	(Reference)	(0.85,4.39)	(1.33,8.11)	
Model 1 (OR)	1.00	1.84	2.35	0.079
	(Reference)	(0.78,4.35)	(0.95,5.81)	
Diabetes Medication(%)	**3.9**	**7.5**	**13.7**	
Unadjusted (OR)	1.00	2.01	3.93	0.001
	(Reference)	(0.83,4.87)	(1.53,10.13)	
Model 1 (OR)	1.00	1.81	2.61	0.049
	(Reference)	(0.72,4.55)	(0.96,7.11)	

Odds ratios (OR) are estimated with generalized logistic regression models. Model 1 is adjusted for sex, age, and race. P trend is calculated with the group ordinal as a continuous variable

Supplementary material: Tables for the association of PTFQI, TT4RI, and TSHI with BMI, obesity, high HbA1c, use of diabetes medication, and diabetes-related deaths in the main sample (N_2=5129).

(Equivalent to Table 2 in the manuscript, which shows the association of TFQI)

Table Main sample - PTFQI. Association of parametric thyroid feedback quantile-based index (PTFQI) with BMI, obesity, high HbA1c, use of diabetes medication, and diabetes-related deaths in the main sample (N_2=5129).

	PTFQI				
	Q1	**Q2**	**Q3**	**Q4**	
	[-1,-0.23)	**[-0.23,-0.01)**	**[-0.01,0.21)**	**[0.21,1]**	**P trend**
N (N_2=5129)	1322	1249	1269	1289	
BMI (kg/m^2)	**28.1**	**28.0**	**29.1**	**28.8**	
Model 1 (dif.)	0.0	0.0	1.1	0.8	0.007
	(Reference)	(-0.6,0.7)	(0.7,1.5)	(0.1,1.5)	
Obesity(%)	**31.1**	**28.9**	**36.5**	**35.9**	
Model 1 (OR)	1.00	0.93	1.32	1.29	0.002
	(Reference)	(0.77,1.12)	(1.15,1.52)	(1.10,1.50)	
HbA1c>=6.5(%)	**5.0**	**6.0**	**9.4**	**10.0**	
Model 1 (OR)	1.00	1.21	1.84	1.70	0.005
	(Reference)	(0.93,1.58)	(1.47,2.30)	(1.24,2.33)	
Model 2 (OR)	1.00	1.11	1.49	1.43	0.041
	(Reference)	(0.86,1.43)	(1.16,1.91)	(1.04,1.98)	
Diabetes Medication(%)	**4.8**	**6.8**	**9.3**	**10.2**	
Model1 (OR)	1.00	1.40	1.78	1.68	0.002
	(Reference)	(0.92,2.13)	(1.30,2.42)	(1.26,2.25)	
Model2 (OR)	1.00	1.30	1.46	1.43	0.027
	(Reference)	(0.87,1.94)	(1.09,1.96)	(1.06,1.92)	
Diabetes-related deaths (n)	**0**	**4**	**8**	**15**	
Crude rate (per 100000 person-years)	**0.0**	**38.8**	**123.3**	**196.2**	
Crude rate (per 100000 person-years)	**19.5**		**159.3**		
Model 1 (RR)	1.00		4.65		0.013#
	(Reference)		(0.97,22.30)		
Model 2 (RR)	1.00		3.84		0.033#
	(Reference)		(0.86,17.19)		
Model 3 (RR)	1.00		3.42		0.103#
	(Reference)		(0.76,15.42)		

Differences, odds ratios (OR), and rate ratios (RR) are estimated with generalized linear, logistic, and Poisson regression models respectively. Model 1 is adjusted for sex, age, and race. Model 2 is further adjusted for BMI. Model 3 is further adjusted for initially presenting HbA1c>=6.5 and using diabetes medication. P trend is calculated with the PTFQI quartile ordinal as a continuous variable except in the models with only 2 categories# in which it is calculated with PTFQI as a continuous variable.

Table Main sample - TT4RI. Association of thyrotroph T4 resistance index (TT4RI) with BMI, obesity, high HbA1c, use of diabetes medication, and diabetes-related deaths in the main sample (N_2=5129).

	TT4RI				
	Q1	Q2	Q3	Q4	
	[lo.,10.6)	[10.6,16.2)	[16.2,24.6)	[24.6,hi.]	P trend
N (N_2=5129)	1364	1262	1238	1265	
BMI (kg/m^2)	**27.9**	**28.1**	**28.7**	**29.2**	
Model 1 (dif.)	0.0	0.3	1.0	1.4	0.002
	(Reference)	(-0.5,1.2)	(0.3,1.6)	(0.6,2.2)	
Obesity(%)	**31.1**	**29.9**	**34.3**	**37.2**	
Model 1 (OR)	1.00	0.98	1.21	1.37	0.011
	(Reference)	(0.76,1.24)	(0.96,1.52)	(1.08,1.73)	
HbA1c>=6.5(%)	**6.0**	**6.8**	**8.3**	**9.2**	
Model 1 (OR)	1.00	1.13	1.34	1.33	0.090
	(Reference)	(0.82,1.57)	(1.03,1.75)	(0.93,1.91)	
Model 2 (OR)	1.00	1.02	1.14	1.07	0.609
	(Reference)	(0.73,1.43)	(0.86,1.52)	(0.73,1.58)	
Diabetes Medication(%)	**6.7**	**7.4**	**7.6**	**9.4**	
Model1 (OR)	1.00	1.08	1.02	1.13	0.491
	(Reference)	(0.82,1.42)	(0.81,1.29)	(0.87,1.47)	
Model2 (OR)	1.00	0.99	0.87	0.92	0.480
	(Reference)	(0.74,1.32)	(0.70,1.09)	(0.68,1.25)	
Diabetes-related deaths (n)	**1**	**6**	**6**	**14**	
Crude rate (per 100000 person-years)	**16.4**	**60.2**	**90.3**	**193.6**	
Crude rate (per 100000 person-years)	**38.5**		**141.7**		
Model 1 (RR)	1.00		2.52		0.012#
	(Reference)		(1.02,6.26)		
Model 2 (RR)	1.00		2.17		0.025#
	(Reference)		(0.92,5.10)		
Model 3 (RR)	1.00		1.89		0.018#
	(Reference)		(0.87,4.12)		

Differences, odds ratios (OR), and rate ratios (RR) are estimated with generalized linear, logistic, and Poisson regression models respectively. Model 1 is adjusted for sex, age, and race. Model 2 is further adjusted for BMI. Model 3 is further adjusted for initially presenting HbA1c>=6.5 and using diabetes medication. P trend is calculated with the TT4RI quartile ordinal as a continuous variable except in the models with only 2 categories# in which it is calculated with ln TT4RI as a continuous variable.

Table Main sample - TSHI. Association of TSH index (TSHI) with BMI, obesity, high HbA1c, use of diabetes medication, and diabetes-related deaths in the main sample (N_2=5129).

	TSHI				
	Q1	**Q2**	**Q3**	**Q4**	
	[lo.,1.41)	**[1.41,1.84)**	**[1.84,2.27)**	**[2.27, hi.]**	**P trend**
N (N_2=5129)	1359	1263	1240	1267	
BMI (kg/m^2)	**27.8**	**28.3**	**28.8**	**29.1**	
Model 1 (dif.)	0.0	0.6	1.2	1.5	0.002
	(Reference)	(-0.2,1.4)	(0.5,1.8)	(0.7,2.3)	
Obesity(%)	**30.1**	**30.7**	**34.2**	**37.5**	
Model 1 (OR)	1.00	1.06	1.26	1.45	0.005
	(Reference)	(0.84,1.33)	(1.00,1.58)	(1.15,1.83)	
HbA1c>=6.5(%)	**5.7**	**6.8**	**8.2**	**9.6**	
Model 1 (OR)	1.00	1.19	1.41	1.44	0.049
	(Reference)	(0.81,1.75)	(1.06,1.89)	(1.01,2.07)	
Model 2 (OR)	1.00	1.03	1.17	1.15	0.391
	(Reference)	(0.71,1.48)	(0.88,1.56)	(0.78,1.69)	
Diabetes Medication(%)	**6.2**	**7.6**	**7.1**	**10.1**	
Model1 (OR)	1.00	1.21	1.03	1.29	0.201
	(Reference)	(0.85,1.71)	(0.83,1.28)	(1.00,1.65)	
Model2 (OR)	1.00	1.06	0.85	1.04	0.893
	(Reference)	(0.76,1.48)	(0.70,1.03)	(0.80,1.35)	
Diabetes-related deaths (n)	**0**	**6**	**7**	**14**	
Crude rate (per 100000 person-years)	**0.0**	**57.1**	**109.3**	**194.0**	
Crude rate (per 100000 person-years)	**28.8**		**151.3**		
Model 1 (RR)	1.00		3.41		0.004[#]
	(Reference)		(1.49,7.80)		
Model 2 (RR)	1.00		2.95		0.010[#]
	(Reference)		(1.35,6.43)		
Model 3 (RR)	1.00		2.72		0.007[#]
	(Reference)		(1.29,5.75)		

Differences, odds ratios (OR), and rate ratios (RR) are estimated with generalized linear, logistic, and Poisson regression models respectively. Model 1 is adjusted for sex, age, and race. Model 2 is further adjusted for BMI. Model 3 is further adjusted for initially presenting HbA1c>=6.5 and using diabetes medication. P trend is calculated with the TSHI quartile ordinal as a continuous variable except in the models with only 2 categories[#] in which it is calculated with TSHI as a continuous variable.

Supplementary material: Tables for the association IN NORMOTHYROID SUBJECTS of TFQI, PTFQI, TT4RI, and TSHI with BMI, obesity, high HbA1c, use of diabetes medication, and diabetes-related deaths.

Table Normothyroid sample - TFQI. Association of thyroid feedback quantile-based index (TFQI) with BMI, obesity, high HbA1c, use of diabetes medication, and diabetes-related deaths in the normothyroid sample (N_3=4750)

	TFQI				
	Q1	**Q2**	**Q3**	**Q4**	
	[-1,-0.25)	**[-0.25,0)**	**[0,0.25)**	**[0.25,1]**	**P trend**
N (N_3=4750)	1208	1173	1188	1181	
BMI (kg/m^2)	**28.1**	**27.9**	**29.0**	**28.8**	
Model 1 (dif.)	0.0	-0.1	1.1	0.8	0.005
	(Reference)	(-0.7,0.6)	(0.7,1.4)	(0.1,1.6)	
Obesity(%)	**30.7**	**28.3**	**36.5**	**35.7**	
Model 1 (OR)	1.00	0.91	1.34	1.28	0.001
	(Reference)	(0.73,1.14)	(1.16,1.54)	(1.11,1.48)	
HbA1c>=6.5(%)	**4.9**	**6.6**	**8.9**	**10.3**	
Model 1 (OR)	1.00	1.31	1.67	1.75	0.002
	(Reference)	(0.97,1.78)	(1.36,2.06)	(1.33,2.31)	
Model 2 (OR)	1.00	1.24	1.37	1.47	0.027
	(Reference)	(0.92,1.65)	(1.07,1.74)	(1.11,1.94)	
Diabetes Medication(%)	**4.7**	**7.4**	**8.5**	**10.2**	
Model1 (OR)	1.00	1.53	1.61	1.72	0.001
	(Reference)	(1.03,2.26)	(1.10,2.35)	(1.37,2.15)	
Model2 (OR)	1.00	1.45	1.32	1.44	0.021
	(Reference)	(1.00,2.12)	(0.92,1.89)	(1.17,1.79)	
Diabetes-related deaths (n)	**0**	**4**	**7**	**14**	
Crude rate (per 100000 person-years)	**0.0**	**41.6**	**115.3**	**192.7**	
Crude rate (per 100000 person-years)	**20.9**		**153.0**		
Model 1 (RR)	1.00		4.29		0.054[#]
	(Reference)		(0.94,19.55)		
Model 2 (RR)	1.00		3.56		0.107[#]
	(Reference)		(0.84,14.94)		
Model 3 (RR)	1.00		3.49		0.312[#]
	(Reference)		(0.82,14.81)		

Differences, odds ratios (OR), and rate ratios (RR) are estimated with generalized linear, logistic, and Poisson regression models respectively. Model 1 is adjusted for sex, age, and race. Model 2 is further adjusted for BMI. Model 3 is further adjusted for initially presenting HbA1c>=6.5 and using diabetes medication. P trend is calculated with the TFQI quartile ordinal as a continuous variable except in the models with only 2 categories[#] in which it is calculated with TFQI as a continuous variable.

Table Normothyroid sample - PTFQI. Association of parametric thyroid feedback quantile-based index (PTFQI) with BMI, obesity, high HbA1c, use of diabetes medication, and diabetes-related deaths in the normothyroid sample (N_3=4750)

	PTFQI				
	Q1	**Q2**	**Q3**	**Q4**	
	[-1,-0.23)	**[-0.23,-0.01)**	**[-0.01,0.21)**	**[0.21,1]**	**P trend**
N (N_3=4750)	1195	1194	1172	1189	
BMI (kg/m^2)	**28.1**	**27.9**	**29.1**	**28.7**	
Model 1 (dif.)	0.0	0.0	1.1	0.7	0.006
	(Reference)	(-0.7,0.7)	(0.7,1.5)	(0.1,1.4)	
Obesity(%)	**30.6**	**28.5**	**36.4**	**35.8**	
Model 1 (OR)	1.00	0.93	1.35	1.30	0.001
	(Reference)	(0.74,1.16)	(1.17,1.55)	(1.12,1.50)	
HbA1c>=6.5(%)	**4.9**	**6.1**	**9.4**	**10.3**	
Model 1 (OR)	1.00	1.23	1.81	1.72	0.008
	(Reference)	(0.92,1.64)	(1.47,2.24)	(1.22,2.41)	
Model 2 (OR)	1.00	1.14	1.48	1.46	0.047
	(Reference)	(0.87,1.50)	(1.18,1.86)	(1.05,2.03)	
Diabetes Medication(%)	**4.6**	**7.1**	**8.7**	**10.4**	
Model1 (OR)	1.00	1.51	1.72	1.79	0.001
	(Reference)	(0.99,2.28)	(1.22,2.43)	(1.36,2.35)	
Model2 (OR)	1.00	1.41	1.41	1.52	0.016
	(Reference)	(0.94,2.11)	(1.02,1.94)	(1.17,1.99)	
Diabetes-related deaths (n)	**0**	**4**	**8**	**13**	
Crude rate (per 100000 person-years)	**0.0**	**40.6**	**132.0**	**176.5**	
Crude rate (per 100000 person-years)	**20.8**		**153.9**		
Model 1 (RR)	1.00		4.26		0.051#
	(Reference)		(0.92,19.62)		
Model 2 (RR)	1.00		3.59		0.108#
	(Reference)		(0.85,15.15)		
Model 3 (RR)	1.00		3.42		0.321#
	(Reference)		(0.81,14.53)		

Differences, odds ratios (OR), and rate ratios (RR) are estimated with generalized linear, logistic, and Poisson regression models respectively. Model 1 is adjusted for sex, age, and race. Model 2 is further adjusted for BMI. Model 3 is further adjusted for initially presenting HbA1c>=6.5 and using diabetes medication. P trend is calculated with the PTFQI quartile ordinal as a continuous variable except in the models with only 2 categories# in which it is calculated with PTFQI as a continuous variable.

Table Normothyroid sample - TT4RI. Association of thyrotroph T4 resistance index (TT4RI) with BMI, obesity, high HbA1c, use of diabetes medication, and diabetes-related deaths in the normothyroid sample (N_3=4750)

	TT4RI				
	Q1	**Q2**	**Q3**	**Q4**	
	[lo.,10.6)	**[10.6,16.2)**	**[16.2,24.6)**	**[24.6,hi.]**	**P trend**
N (N_3=4750)	1186	1240	1223	1101	
BMI (kg/m^2)	**27.9**	**28.1**	**28.7**	**29.1**	
Model 1 (dif.)	0.0	0.3	0.9	1.4	0.002
	(Reference)	(-0.5,1.2)	(0.3,1.6)	(0.6,2.2)	
Obesity(%)	**30.8**	**29.5**	**34.3**	**36.9**	
Model 1 (OR)	1.00	0.97	1.21	1.35	0.009
	(Reference)	(0.75,1.24)	(0.97,1.51)	(1.07,1.72)	
HbA1c>=6.5(%)	**5.9**	**6.8**	**8.4**	**9.6**	
Model 1 (OR)	1.00	1.11	1.31	1.34	0.105
	(Reference)	(0.78,1.59)	(0.98,1.73)	(0.91,1.98)	
Model 2 (OR)	1.00	1.02	1.13	1.09	0.551
	(Reference)	(0.70,1.48)	(0.83,1.54)	(0.73,1.63)	
Diabetes Medication(%)	**6.5**	**7.4**	**7.6**	**9.3**	
Model1 (OR)	1.00	1.07	0.99	1.08	0.734
	(Reference)	(0.79,1.43)	(0.78,1.26)	(0.83,1.40)	
Model2 (OR)	1.00	0.98	0.85	0.88	0.301
	(Reference)	(0.71,1.35)	(0.66,1.11)	(0.64,1.20)	
Diabetes-related deaths (n)	**1**	**6**	**6**	**12**	
Crude rate (per 100000 person-years)	**18.6**	**61.0**	**91.3**	**183.4**	
Crude rate (per 100000 person-years)	**41.2**		**134.4**		
Model 1 (RR)	1.00		2.11		0.081$^{\#}$
	(Reference)		(0.80,5.57)		
Model 2 (RR)	1.00		1.84		0.116$^{\#}$
	(Reference)		(0.73,4.64)		
Model 3 (RR)	1.00		1.49		0.193$^{\#}$
	(Reference)		(0.58,3.83)		

Differences, odds ratios (OR), and rate ratios (RR) are estimated with generalized linear, logistic, and Poisson regression models respectively. Model 1 is adjusted for sex, age, and race. Model 2 is further adjusted for BMI. Model 3 is further adjusted for initially presenting HbA1c>=6.5 and using diabetes medication. P trend is calculated with the TT4RI quartile ordinal as a continuous variable except in the models with only 2 categories$^{\#}$ in which it is calculated with ln TT4RI as a continuous variable.

Table Normothyroid sample - TSHI. Association of TSH index (TSHI) with BMI, obesity, high HbA1c, use of diabetes medication, and diabetes-related deaths in the normothyroid sample (N_3=4750).

	TSHI				
	Q1	**Q2**	**Q3**	**Q4**	
	[lo.,1.41)	**[1.41,1.84)**	**[1.84,2.27)**	**[2.27, hi.)**	**P trend**
N (N_3=4750)	1181	1242	1225	1102	
BMI (kg/m^2)	**27.8**	**28.2**	**28.8**	**29.0**	
Model 1 (dif.)	0.0	0.6	1.1	1.4	0.002
	(Reference)	(-0.2,1.3)	(0.5,1.8)	(0.6,2.2)	
Obesity(%)	**29.8**	**30.2**	**34.2**	**37.2**	
Model 1 (OR)	1.00	1.05	1.27	1.44	0.004
	(Reference)	(0.83,1.32)	(1.02,1.57)	(1.14,1.82)	
HbA1c>=6.5(%)	**5.5**	**6.8**	**8.3**	**10.1**	
Model 1 (OR)	1.00	1.18	1.38	1.46	0.061
	(Reference)	(0.78,1.76)	(1.00,1.91)	(0.99,2.15)	
Model 2 (OR)	1.00	1.03	1.16	1.18	0.351
	(Reference)	(0.69,1.53)	(0.83,1.61)	(0.79,1.76)	
Diabetes Medication(%)	**6.0**	**7.6**	**7.2**	**10.1**	
Model1 (OR)	1.00	1.19	1.02	1.25	0.273
	(Reference)	(0.83,1.70)	(0.80,1.29)	(0.99,1.58)	
Model2 (OR)	1.00	1.05	0.85	1.01	0.706
	(Reference)	(0.73,1.51)	(0.66,1.08)	(0.78,1.31)	
Diabetes-related deaths (n)	**0**	**6**	**7**	**12**	
Crude rate (per 100000 person-years)	**0.0**	**57.8**	**110.5**	**184.0**	
Crude rate (per 100000 person-years)	**30.8**		**144.7**		
Model 1 (RR)	1.00		2.83		0.038#
	(Reference)		(1.14,7.05)		
Model 2 (RR)	1.00		2.48		0.055#
	(Reference)		(1.04,5.96)		
Model 3 (RR)	1.00		2.14		0.113#
	(Reference)		(0.85,5.39)		

Differences, odds ratios (OR), and rate ratios (RR) are estimated with generalized linear, logistic, and Poisson regression models respectively. Model 1 is adjusted for sex, age, and race. Model 2 is further adjusted for BMI. Model 3 is further adjusted for initially presenting HbA1c>=6.5 and using diabetes medication. P trend is calculated with the TSHI quartile ordinal as a continuous variable except in the models with only 2 categories# in which it is calculated with TSHI as a continuous variable.

Supplementary material: Sensitivity analysis: manuscript's Table 2 with further adjustments.

Adjusted Table 2: adjusted for education, physical activity, and sedentary time. Association of thyroid feedback quantile-based index (TFQI) with BMI, obesity, high HbA1c, use of diabetes medication, and diabetes-related deaths in the main sample ($N_{2'}$=5105).

	TFQI				
	Q1	**Q2**	**Q3**	**Q4**	
	[-1,-0.25)	**[-0.25,0)**	**[0,0.25)**	**[0.25,1]**	**P trend**
N ($N_{2'}$=5105)	1315	1255	1263	1272	
BMI (kg/m2)	**28.1**	**28.0**	**29.1**	**28.8**	
Model 1 (dif.)	0.0	0.0	1.0	0.8	0.021
	(Reference)	(-0.6,0.6)	(0.6,1.4)	(0.0,1.5)	
Obesity(%)	**31.0**	**28.9**	**36.7**	**35.9**	
Model 1 (OR)	1.00	0.91	1.32	1.26	0.009
	(Reference)	(0.74,1.12)	(1.13,1.53)	(1.07,1.48)	
HbA1c>=6.5%(%)	**5.0**	**6.3**	**8.9**	**10.0**	
Model 1 (OR)	1.00	1.28	1.74	1.73	0.006
	(Reference)	(0.96,1.69)	(1.38,2.20)	(1.32,2.27)	
Model 2 (OR)	1.00	1.19	1.41	1.45	0.047
	(Reference)	(0.91,1.55)	(1.09,1.84)	(1.09,1.92)	
Diabetes Medication(%)	**4.8**	**7.1**	**9.2**	**9.9**	
Model1 (OR)	1.00	1.44	1.71	1.63	0.006
	(Reference)	(0.99,2.07)	(1.19,2.47)	(1.29,2.06)	
Model2 (OR)	1.00	1.35	1.42	1.38	0.053
	(Reference)	(0.96,1.91)	(0.99,2.02)	(1.10,1.74)	
Diabetes-related deaths (n)	**0**	**4**	**7**	**15**	
Crude rate (per 100000 person-years)	**0.0**	**39.1**	**109.3**	**208.2**	
Crude rate (per 100000 person-years)	**19.5**		**157.9**		
Model 1 (RR)	1.00		4.66		0.027#
	(Reference)		(1.01,21.54)		
Model 2 (RR)	1.00		3.89		0.075#
	(Reference)		(0.87,17.32)		
Model 3 (RR)	1.00		3.35		0.205#
	(Reference)		(0.76,14.73)		

Differences, odds ratios (OR), and rate ratios (RR) are estimated with generalized linear, logistic, and Poisson regression models respectively. Model 1 is adjusted for sex, age, race, education (less, equal, or more than high school graduate), physical activity (less than moderate, moderate, vigorous), and sedentary time/day. Model 2 is further adjusted for BMI. Model 3 is further adjusted for initially presenting HbA1c>=6.5% and using diabetes medication. P trend is calculated with the TFQI quartile ordinal as a continuous variable except in the models with only 2 categories# in which it is calculated with TFQI as a continuous variable.