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Higher Parametric Thyroid Feedback Quantile-based Index is a predictor of type 2 diabetes in a German population sample.

Higher PTFQI predicts incident type 2 diabetes in Germans.

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KEYWORDS: Type 2 diabetes; Pituitary sensitivity; Thyroid axis.

Abstract

BACKGROUND. Type 2 diabetes has been described to be associated with hypothyroidism but we recently found that a decrease in pituitary sensitivity to thyroid hormone is associated with diabetes, obesity, and the metabolic syndrome. We aim to assess the longitudinal nature of this association in the population-based Study of Health in Pomerania(SHIP) in Germany.

MATERIALS AND METHODS. 77% of a population-based sample of 4308 participants between 20 and 79 years was followed for 5 years. We studied 2542 participants without diabetes or thyroid medication at baseline and complete data in the variables of interest. Data of baseline thyroxine(fT4) and thyrotropin(TSH) were used to calculate the Parametric Thyroid Feedback Quantile-based Index(PTFQI), which measures whether TSH remains elevated despite fT4 being high. It uses the average population response as reference. PTFQI association with incidence of type 2 diabetes over 5 years was estimated with Poisson regression models adjusted for age, sex, and body mass index(BMI).

RESULTS. Compared with the 1st PTFQI quartile, Incidence Rate Ratios (IRR) for diabetes were 1.54(95% CI 0.97 to 2.46), 1.55(0.94 to 2.57), and 1.97(1.27 to 3.10) for the upper quartiles (p-trend=0.004) after adjusting for age and sex. The association remained statistically significant after additionally adjusting for BMI: 1.64(1.05 to 2.59) for the 4th vs the 1st quartile (p-trend=0.043).

CONCLUSIONS. An elevation of the pituitary TSH-inhibition threshold is associated with incident type 2 diabetes independently of BMI. The PTFQI might have clinical potential for prognosis and metabolic status monitoring.

Introduction

Type 2 diabetes development is associated with thyroid disorders, mostly with those that manifest as hypothyroidism[1], but also with some forms of hyperthyroidism[2]. Apart from shared immunity-related processes related to several clinical thyroid diseases, hypothyroidism is linked with diabetes mainly through decreased insulin-stimulated muscle glucose uptake[3,4], and decreased oxidation in hypo-functional mitochondria[5] in the context of metabolism slowdown. Even within normal thyroxine (fT4) and thyroid-stimulating hormone (TSH) levels, high-normal TSH associates with metabolic syndrome[6]. Nonetheless, at the population level there is an association between hyperthyroxinemia and prevalent and incident type 2 diabetes[7], which precludes understanding the link between these diseases.

Secretion in the thyroid gland is driven from the hypothalamic-pituitary axis, which is inhibited by thyroid hormone forming a negative feedback loop. Based on hormone levels, it is possible to quantify the inhibition through indexes, such as the Parametric Thyroid Feedback Quantile-based Index (PTFQI) (see below for calculation method), which was recently developed to improve measurement of the thyroid pituitary TSH-inhibition threshold among the general population while other thyroid resistance indices focus on detecting disease conditions [8]. We recently described a cross-sectional coincidence of a decrease in pituitary sensitivity to thyroid hormone (factually an elevation of the regulatory TSH-inhibition threshold) with diabetes, obesity, and the metabolic syndrome[8]. The pituitary TSH-inhibition threshold is not a static number or “point” but an equilibrium between TSH secretion and thyroid hormone and their effects. Reduced effects of thyroid hormone in the pituitary, i.e., a reduced sensitivity, implies an uninhibited TSH secretion and a simultaneous rise of both, TSH and thyroid hormone; thus, an elevated TSH-inhibition threshold. An unanswered key question with respect to this association of diabetes and pituitary resistance to thyroid hormone is the temporal sequence, a prerequisite for investigating causality and potential uses for prognosis and prevention.

In this work, we aim to describe whether a high pituitary TSH-inhibition threshold predicts incident type 2 diabetes at the population level in the Study of Health in Pomerania (SHIP) in Germany.

Materials and methods

Design and subjects

This study analyzes incidence of clinically detected diabetes. We performed a longitudinal analysis of data from the Study of Health in Pomerania (SHIP), a population-based cohort from Northeast Germany[9]. Between 1997 and 2001, a random sample of 4308 participants between 20 and 79 years of age, drawn from the general population, were examined. A follow-up examination performed between 2002 and 2006 revisited 3300 subjects. The study was approved by the local Ethics Committee, all subjects gave informed written consent and all examinations followed the recommendations of the Declaration of Helsinki.

For the current analysis we excluded 285 individuals taking thyroid medication at baseline and 457 individuals with missing data in any of the considered variables at baseline, leaving 3566 participants. Note that some of these participants had abnormal values in fT4 or TSH, that were previously unknown, and which was not an exclusion criterion at this point. Longitudinal analyses were performed after excluding 256 individuals having type 1 or type 2 clinically detected diabetes at baseline and 768 individuals without follow-up data, resulting in a study sample of 2542 individuals (Supplementary Figure 1 - Flowchart)[10].

Laboratory data

The study analyzed non-fasting blood samples in the central laboratory of the University Medicine Greifswald. Serum fT4 and TSH were measured by a homogeneous, sequential, chemiluminescent immunoassay based on LOCI technology (Dimension Vista System Flex reagent cartridge, Siemens Healthcare Diagnostics Inc., Newark, DE, USA). Glycated hemoglobin (HbA1c) levels were measured by high-performance liquid chromatography (Bio-Rad Diamat, Munich, Germany).

The assay-specific reference normality cutoffs for serum fT4 were 11.2 and 18.0 pmol/L (0.87 and 1.40 ng/dL) and for serum TSH were 0.26 mIU/L and 2.69 mIU/L.

Parametric Thyroid Feedback Quantile-based Index (PTFQI)

The Thyroid Feedback Quantile-based Index quantifies deviations from the median pituitary response (inhibition) to thyroid hormone [8]. Conceptually, it compares ranks (order position from minimum to maximum value) of fT4 and TSH, that are subtracted one from the other once converted to quantiles (range 0 to 1), considering TSH in decreasing order (fT4 and TSH are inversely correlated). In the parametric version of this index[11], the conversion is achieved by applying the standard normal cumulative distribution function using the descriptive population values for fT4 and TSH, which allows tailoring the formula for specific regional ranges (and measurement methods). The index ranges between -1 and 1. Negative values indicate higher TSH inhibition by fT4 than that expected (higher pituitary sensitivity, i.e. lower TSH-inhibition threshold) and positive values, higher TSH concentration than that expected for fT4 concentration (lower pituitary sensitivity, i.e. higher TSH-inhibition threshold). To calculate PTFQI we applied the following formula $\Phi((\mathrm{fT4}-\mu_{\mathrm{fT4}})/\sigma_{\mathrm{fT4}})-(1-\Phi((\ln \mathrm{TSH}-\mu_{\ln\ \mathrm{TSH}})/\sigma_{\ln\ \mathrm{TSH}}))$, where μ_{fT4}=14.297 pmol/L, σ_{fT4}=2.246 pmol/L (μ_{fT4}=1.111 ng/dL, σ_{fT4}=0.175 ng/dL), $\mu_{\ln\ \mathrm{TSH}}$=-0.3123 ln mIU/L, and $\sigma_{\ln\ \mathrm{TSH}}$=0.9423 ln mIU/L for the German population as measured in SHIP. This formula can be easily implemented in spreadsheet programs (for a detailed description of the calculation and the interpretation of PTFQI, see Alonso-Ventura et al. Thyroid 2022. Supplementary Material, openly available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9807248/bin/Supp_Data.pdf) [8,11].

We also calculated other thyroid resistance indices (the TSH Index [12] and the Thyrotroph Thyroid Hormone Sensitivity Index[13]) for comparison.

Clinical data

Computer-assisted personal interviews were used to collect data on age, sex, type 1 and type 2 diabetes, and current medication in both examinations. Relevant Anatomical Therapeutic Chemical (ATC) codes used for medication classification were H03 - thyroid medication, A10 - anti-diabetic medication, A10A - insulin, and A10BA02 - metformin. Height and weight were measured and used to calculate body mass index (BMI), which served to classify participants into normal weight (<25 Kg/m^2, including lowest values), overweight (≥ 25 Kg/m^2 and <30 Kg/m^2), class I obesity (≥ 30 Kg/m^2 and <35 Kg/m^2), and class II and III obesity (≥ 35 Kg/m^2) strata.

Endpoint definition

Diabetes was defined at each examination as patients reporting a previous medical diagnosis of type 2 diabetes and/or taking anti-diabetic medication. The study non-fasting blood samples precluded using glucose as diagnostic criterion. The variable "taking anti-diabetic medication" was analyzed as a "hard" proxy of incident diabetes when it identified new onset of medication, more robust than the variable that used only reported data. At the time of data collection, the only reason for being prescribed anti-diabetic medication in the cohort participants was having a diabetes diagnosis.

Statistical analyses

Continuous variables were described as mean and SD and categorical variables as percentage and count. TSH, which is skewed to the right, was log transformed for analyses.

In the cross-sectional-analyses, PTFQI quartiles association with prevalent type 2 diabetes at baseline was studied with logistic regression models, used to calculate odds ratios (ORs). Once prevalent diabetes cases were removed, in a scatter-plot of TSH versus fT4 we plotted PTFQI octiles and highlighted cases of incident type 2 diabetes. In the longitudinal analyses, for each PTFQI quartile we calculated type 2 diabetes incidence at follow-up. Poisson regressions served to model and test the association, calculating incidence rate ratios (IRRs), referenced to the first PTFQI quartile, after adjusting for age and sex (model 1). Inverse probability weights were applied to account for selection bias due to loss to follow-up in all follow-up regressions and calculated incidence rates. A test for trend was performed entering the quartile as number in the regression. PTFQI is high in obesity and thus BMI could be a potential confounder. A model additionally adjusting for baseline BMI (model 2) was created to test for independence and to understand how PTFQI and BMI are related with incident type 2 diabetes. Regressions were also performed in a sample restricted to euthyroid participants. All these analyses were also performed with new onset of anti-diabetic medication as endpoint.

HbA1c was not a diagnostic criterion for diabetes at the time of data collection, and it was not available for all patients and visits. As sensitivity analyses, we excluded at baseline those participants with HbA1c ≥ 6.5% and examined incidence of clinically detected diabetes and incidence of undetected participants with HbA1c ≥ 6.5%.

All analyses were performed with statistical computing software R version 3.4.4.

Results

At baseline, PTFQI was associated with age, sex, and BMI (Table 1). Type 2 diabetes was cross-sectionally associated with PTFQI categorized in quartiles (Table 1) and as a continuous variable after adjusting for age and sex (p=0.003) and additionally for BMI (p=0.031). In this sample, PTFQI was cross-sectionally associated with BMI at baseline, increasing 0.043 (0.016, 0.070) per 10 kg/m^2, adjusted for age and sex. After excluding prevalent cases of type 1 or type 2 diabetes and participants with loss-to-follow-up, the remaining 2542 participants (50.0% men) mean (SD) age was 47.7 (15.1) years (Supplementary Table 1)[10]. Among them, 113 new cases of type 2 diabetes occurred during the 5 years of median follow-up time (13420 person-years).

Participants developed type 2 diabetes at different rates across the fT4 and TSH joint distribution (Figure 1). Type 2 diabetes incidence increased across PTFQI quartiles, that is, with higher pituitary TSH-inhibition thresholds (pituitary resistance to fT4). Compared with the 1st quartile, IRRs were 1.54 (95% CI 0.97, 2.46), 1.55 (0.94, 2.57), and 1.97 (1.27, 3.10) for the 2nd, 3rd, and 4th quartiles respectively (p trend = 0.004) after adjusting for age and sex (Table 2). The association of PTFQI with incident type 2 diabetes was still statistically significant after adjusting for BMI: 1.64 (1.05, 2.59) for the 4th vs the 1st quartile (p trend = 0.043). These effects, with similar or even stronger magnitude, were found for the alternative analysis end-point, the onset of anti-diabetic medication (Table 2).

To explore PTFQI and BMI contributions in the development of type 2 diabetes they were both introduced as continuous variables in models, separately and together. When considered in a separate model (adjusted for age and sex) each one unit increase in PTFQI was related with an IRR for type 2 diabetes of 1.95 (1.16, 3.27) and each unit of BMI, with an IRR of 1.14 (1.10, 1.17). When considered in one single model, i.e. mutually adjusted, PTFQI coefficient was reduced, but still conserved 73.1% of the strength of association, and BMI coefficient was almost identical, being reduced only in 2.6%. Finally, we explored PTFQI effect on type 2 diabetes incidence across obesity strata. We observed a tendency for a progressively reduced effect at more severe obesity categories (interaction term statistically non-significant). Interestingly, a one-unit higher PTFQI among normal weight participants represented a similar risk for type 2 diabetes to that of obese individuals (with high or low PTFQI) (Figure 2).

Analyses performed on euthyroid individuals with fT4 and TSH within the normal ranges (N=2215) showed similar association strengths and gradient across PTFQI quartiles, although statistical significance could not be proven in all tests. This was mainly due to lower number of participants and incident cases: diabetes incidence was similar between those with abnormal values that indicate high or low thyroid function, thus these groups, which were excluded, were not driving the association described in the non-restricted analysis (Supplementary Table 2)[10].

Analyses of association of other thyroid resistance indices (TSH index and Thyrotroph Thyroid Hormone Sensitivity Index) showed similar trends but statistical significance was not reached in all tests and the dose-response showed lower linearity (Supplementary Table 3, Supplementary Table 4)[10]. After excluding participants with HbA1c ≥ 6.5% at baseline (Supplementary Table 5)[10], PTFQI showed a stronger association with clinically detected incident diabetes (Table 3), but the reduced number of incident cases precluded demonstrating significance in stratified analyses (Supplementary Table 6, Supplementary Figure 2, Supplementary Figure 3)[10].

Additional models showed similar results and were included in supplementary material (Supplementary Table 7)[10].

As an exploratory analysis, sex interaction was modelled. PTFQI associations with diabetes seemed to be stronger in men than in women, but given the small number of incident cases, especially among women, the results are not reliable and this model is not included here.

Discussion

In this longitudinal cohort study of 2542 participants from Germany we demonstrate, for the first time, that an elevation in the pituitary TSH-inhibition threshold is associated with incident type 2 diabetes in the next five years and that this effect is independent of BMI. Measurement of this TSH-inhibition threshold with PTFQI could potentially provide prognostic information.

Previous studies on the relationship between thyroid function and type 2 diabetes provided mixed results, mostly showing that hypothyroidism, in the clinical[1] or subclinical[6] condition, predispose to type 2 diabetes and metabolic syndrome. At the other extreme of the thyroid function, recent reports also linked hyperthyroxinemia[7,14] with prevalent and incident type 2 diabetes. Incidentally, thyrotoxicosis may trigger ketoacidosis in diabetic patients[15]. The mechanisms involved in that event (mainly increased hepatic glucose output through catecholamines sensitization) seem of minor importance in non-diabetic patients with thyroid hormones within the normal range. However, we recently described in a U.S. population that diabetes is more prevalent when both commonly used thyroid laboratory measurements, fT4 and TSH, are elevated, even within the normal range[8]. Those cross-sectional results have been confirmed in independent populations: a Spanish one[11] and a middle-east one [16]. Here, we replicate those cross-sectional results in yet another sample from an independent European population and, in addition, we demonstrate that the same situation precedes and is associated with the onset of type 2 diabetes.

Clinical thyroid disease, in particular hypothyroidism, is associated with increased mortality from diabetes and cardiovascular disease among women, in whom thyroid diseases are more prevalent than in men[17]. Subclinical hypothyroidism is also associated with coronary heart disease morbidity and mortality[18] and, even within normal ranges, high-normal TSH, which is usually interpreted as low thyroid function, is associated with increased cardiovascular death risk in the U.S. population[19]. However, we showed that, in the U.S. population, diabetes-related deaths occurred more often among those with high PTFQI, which identifies those subjects who had not only high-normal TSH but also high-normal fT4[8], supporting the temporal precedence of the concurrently altered thyroid measurements. Certainly, a more detailed interpretation of the relationship of these thyroid parameters with diabetes is needed.

This situation of high fT4 and TSH resembles the impaired central inhibitory response to fT4 that occurs in genetic syndromes of resistance to thyroid hormone[20]. Alternatively, it also might mean that in these individuals a higher thyroid stimulus is generated from the central nervous system. Therefore, this condition could be regarded either as an acquired form of central resistance to thyroid hormone or as an elevation of the pituitary TSH-inhibition threshold.

Obesity, one of the main causes of type 2 diabetes, bears changes in the thyroid axis. It is associated with increased levels of TSH[21], which at first glance can be interpreted as linked with lower thyroid function, but elevation of triiodothyronine, and less frequently fT4, has also been reported[22]. Obesity is also more prevalent when there is a concomitant elevation of TSH and fT4[8]. Both hormones are found to be high among morbidly obese individuals[23]. Moreover, weight gain is associated with simultaneous TSH increases while being independent of baseline TSH concentrations in the Framingham Offspring Study cohort[21]. Thus, it could be inferred that it is obesity what changes the thyroid regulation axis[24], or that at least an interdependent loop exists, given the indisputable effect of thyroid hormone on weight[25,26]. Furthermore, it has been demonstrated that bariatric surgery decreases fT4 and TSH in euthyroid patients with obesity and type 2 diabetes[27], and that weight loss with diet and exercise also produces a decrease in TSH in obese children[28] and women[29], or even a decrease in both, thyroid hormone and TSH, in obese girls[30], while weight gain during treatment of girls with anorexia nervosa increased thyroid hormone and TSH[30].

All this evidence suggests a potential causal sequence: in obesity, high TSH could be signaling for an increase in thyroid gland activity[31], rather than compensating a decrease of it. In this regard, it could be interpreted that the central regulation *tries* to compensate a *relative* deficit of thyroidal effects (at least with respect to energy balance) by modifying the TSH-inhibition threshold upwards. A mechanism that has been proposed to explain this effect of obesity on the axis is leptin-induced hypothalamic TSH releasing hormone (TRH) secretion[32]. Downstream, the thyroid stimulus could promote the increased resting metabolic rate observed in obese patients[33] through browning of adipose tissue[34] and uncoupling of the respiratory chain[35]. Another potential explanation would be that obese patients suffer from an acquired thyroid hormone resistance: among genetic thyroid hormone resistance syndromes, TSH inhibition by thyroid hormone is impaired in the central nervous system[8]. In agreement with this concept, among obese subjects, it has been described a reduced number of thyroid hormone receptors in peripheral mononuclear blood cells[36] and in adipose tissue[37], which could be a coherent cause of insufficient fat catabolism in obesity. Besides the number of receptors and their affinity, there are other signaling stages at which several obesity-related factors can impair thyroid hormone actions [38]: hormone membrane transport, activation and deactivation by deiodinases, and interaction with nuclear receptors. The information on the status of these mechanisms in obesity is limited and with multiple regulation loops, like the receptor expression increase observed in mononuclear blood cells in hypothyroidism[36], or the increase in the number of receptors triggered by bariatric surgery, in adipose tissue[33], and by fasting, in blood cells[32]. So, it is difficult at this time to integrate some of this discordant information, in a unified pathophysiological model. We found that the TSH-inhibition threshold elevation, compatible with a central resistance to thyroid hormone, happens not only in obesity, but also in those prone to develop type 2 diabetes, and it happens independently of their BMI. Thus, this central stimulus for the axis must originate form additional mechanisms besides the leptin one mentioned above. Our results are not appropriate for clarifying whether peripheral resistance to thyroid hormone co-exist in obese and type 2 diabetes-prone individuals, which remains a potential possible explanation.

Despite most of the previous knowledge on this topic is focused on obesity, we found that approximately three quarters of the observed effect of the thyroid TSH-inhibition threshold elevation on incident type 2 diabetes is independent from BMI. Remarkably, also the effect seems to be more intense among normal-weight individuals, among who, PTFQI measurement could be used to detect susceptibility to diabetes. Elevation of the TSH-inhibition threshold, according to our results, does not seem to be an intermediate step between obesity and type 2 diabetes, as adjusting for it barely modifies the estimated effect of obesity. On the contrary, obesity partly explains the effect of high PTFQI, although we still found a substantial independent effect on type 2 diabetes incidence. A compatible explanation can be that PTFQI marks a metabolic state that sets individuals at risk of developing both type 2 diabetes and obesity, the latter also increasing the risk of diabetes itself. That is also supported by our observation that the increase of type 2 diabetes predicted by higher PTFQI is maximum among lean subjects and that higher degrees of obesity mutes the association. There is potential diagnostic and prognostic value in taking advantage of the complex information conveyed in the regulation of the hypothalamic-pituitary-thyroid axis[39] and some experts claim that thyroid measurements should be used beyond merely applying pathological thresholds[40]. An index like PTFQI that informs on the status of the negative feedback loop could serve to evaluate the stress on energy balance. Our results are a first hint of potential prognostic utility of PTFQI. Furthermore, during a weight loss program aimed to obese children and adolescents, those in whom a decrease in serum TSH was observed also experimented an improvement in insulin resistance, independently of their change in weight, which in turn was not a statistically significant predictor of the improvement[41]. In summary, PTFQI might also potentially monitor whether interventions for metabolic prevention are being successful.

Thus, speculating a matter that should be discerned by future research, potential clinical applications of PTFQI may include diagnosis of pro-diabetic conditions, prognosis of morbidities and survival, control of patients' evolution, and monitoring of the success of treatments.

PTFQI is a relatively recent index that was defined by our team to be more robust to distorted data and more suitable to study thyroid feedback in the general population than other thyroid resistance indices, which focus on detection of disease conditions. In this study we found that other indices showed a similar trend of association but PTFQI had a more linear dose response and could demonstrate statistical significance in most analyses.

Among the strengths of this study, it is worth mentioning the sample size, representativeness of the population, and a high level of quality assurance and data management. This study also has some limitations that merit consideration when interpreting our results. In the first place, there might be residual confounding in our association estimates. We acknowledge that there is heterogeneity in life-long evolution of fT4 and TSH across populations, which shows in this report from a German cohort as a downwards trend of PTFQI across life, inverse from the previous finding in the US population[8] and in a Spanish sample[11], however it is unlikely to have affected our inferences because all our analyses were adjusted for age. The distribution of TSH across age and countries may differ according to history of iodine status. In SHIP there was a decline of TSH with age, because of the long-term iodine deficiency during middle of the 90s[42].

Also, we could not base diabetes diagnosis in glucose measurement, because blood sampling was without a fasting requirement and also only one blood draw was performed. Type 2 diabetes identification was based on reported physician diagnoses and anti-diabetic medication use, which may have reduced detection sensitivity. Self-report was internally validated by adding information on self-reported treatment and self-reported age at diagnosis, but undiagnosed cases of Type 2 diabetes are frequent (30 to 50%) in Europe, including Germany[43]. However, reports specificity is generally high, above 97%, and accuracy, when combined with treatment information, is deemed sufficient for epidemiologic studies[44]. We assume that physician diagnoses occurred in more severe diabetes cases while undiagnosed diabetes represented milder disease. PTFQI was strongly associated with the incidence of the former, and few undiagnosed participants appeared in the highest PTFQI quartile. Also, 23% of participants were lost-to-follow-up which might have affected the results, despite being a normal attrition rate in cohort studies. Blood draw timing differences across participants may have introduced some noise in thyroid measurements, drawing the association magnitude towards the null, which was not enough to deter out study from finding the described associations. Finally, we describe only the initial central aspect of the complex regulation system, which, on the one hand is useful and convenient because the measurements that we present are readily available in all thyroid laboratories but on the other hand limits the extent to which we can explain mechanistically our observations.

Conclusions

In conclusion, an elevation of the pituitary TSH-inhibition threshold, as measured by PTFQI, is associated with incident type 2 diabetes independently of baseline BMI, in this longitudinal study. These measurements have the potential to provide clinically relevant information for prognosis and metabolic status monitoring.

Declarations

Ethics approval and consent to participate: The SHIP study was approved by the local Ethics Committee.

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Consent for publication: This manuscript does not include details, images, or videos relating to an individual person, requiring specific consent.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors have no conflicts of interest regarding this work. All authors have completed the Conflict of Interest form and declare: the authors had financial support for the submitted work as specified in the acknowledgment section but the funding institutions did not have any role in the writing of the manuscript or the decision to submit it for publication; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Authors' contributions: ML conceptualized the research question and designed the study. ML and TI performed the statistical data analysis. ML, VA-V, FC, and TI interpreted the results and ML and TI wrote the manuscript. SS, JL-B, MD, PT-A, HV, and MN revised the manuscript for important intellectual content. SS, MD, HV, MN, and TI participated in the SHIP study design, data collection, and data management. All authors approved the final version of the manuscript for publication.

None of the material has been published or is under consideration elsewhere.

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Figure Legends

Figure 1. Footnote: Scatterplot: Dots represent observations. Red dots represent participants who developed type 2 diabetes during follow-up. Grey dashed vertical and horizontal straight lines mark fT4 and TSH normality ranges. Black dashed curves represent the 12.5th, 25th, 37.5th, 50th, 62.5th, 75th, and 87.5th percentiles of PTFQI dividing the sample in 8 equal parts. Inner plot: The bar height and the number at the base show crude type 2 diabetes incidence rates (weighted for loss to follow-up) for each PTFQI interval in cases per 10^4 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 cases (i.e., the count of red dots in the scatterplot). Central bars have been fused for visualization purposes (original bars as dashed ghost-bars) because the interval limits are numerically very close to the median and the incidence difference between them conveyed little meaningful information about the association.

N, number of participants; fT4, free Thyroxine; TSH, Thyroid-Stimulating Hormone; PTFQI, Parametric Thyroid Feedback Quantile-based Index; P *number*, Percentile *number*.

Figure 2. Footnote: Estimations from a single Poisson regression model with PTFQI as a continuous variable, interaction terms with obesity strata, adjusted for age and sex, and weighted for loss to follow-up. Risk of normal weight participants at lower PTFQI is used as reference.

PTFQI: Parametric Thyroid Feedback Quantile-based Index; n/N: number of new cases/number at risk; IRR: Incidence Rate Ratio.

Tables

Table 1: Baseline characteristics of the sample and cross-sectional association with type 2 diabetes.

	All	**PTFQI quartiles**				**p**
		1st	**2nd**	**3rd**	**4th**	
		[min.,-0.19)	**[-0.19,0.00)**	**[0.00,0.22)**	**[0.22,max.]**	
N	3566	892	891	893	890	
fT4 (pmol/L)	14.31(2.12)	12.78(1.26)	13.95(2.69)	14.58(1.46)	15.93(1.38)	-
fT4 (ng/dL)	1.11(0.16)	0.99(0.10)	1.08(0.21)	1.13(0.11)	1.24(0.11)	-
TSH (mIU/L)	1.05(2.34)	0.54(0.28)	1.18(4.44)	1.15(1.08)	1.34(0.78)	-
Age (years)	49.3(16.4)	50.5(15.3)	49.2(16.1)	49.7(16.5)	47.9(17.7)	0.006
Sex (male)	50.93[1816]	56.50[504]	48.26[430]	51.06[456]	47.87[426]	0.001
Waist circumference (cm)	88.98(13.85)	89.22(13.11)	88.25(13.76)	89.33(13.90)	89.13(14.58)	0.263
BMI (Kg/m^2)	27.12(4.68)	26.86(4.31)	26.86(4.49)	27.29(4.79)	27.45(5.07)	0.046
Glucose (spot) (mmol/L)	5.61(1.62)	5.65(1.50)	5.55(1.42)	5.60(1.54)	5.66(1.97)	0.003
HbA1c (%)	5.40(0.89)	5.41(0.84)	5.37(0.84)	5.40(0.89)	5.42(0.97)	0.522
Type 2 diabetes	6.98[249]	6.17[55]	6.06[54]	6.38[57]	9.33[83]	0.018
OR (model 1)		1.00	1.05	1.05	1.78	
		(reference)	(0.71, 1.56)	(0.71, 1.55)	(1.23, 2.57)	
OR (model 2)		1.00	1.02	0.97	1.60	
		(reference)	(0.69, 1.52)	(0.65, 1.44)	(1.11, 2.32)	

Cells show mean(sd) or percentage[count]. Statistics are unweighted. P values are test for heterogeneity (not for trend) from unadjusted differences in median (Kruskal-Wallis test) and chi-squared tests. Odds Ratio estimations and 95% CI from logistic regression models. Model 1 adjusted for age and sex, model 2 additionally adjusted for BMI.

Table 2: Incidence of type 2 diabetes and related conditions across pituitary set-points for the thyroid axis measured with PTFQI.

	PTFQI quartiles				
	1st	**2nd**	**3rd**	**4th**	**p trend**
	[min.,-0.19)	**[-0.19,0.00)**	**[0.00,0.22)**	**[0.22,max.]**	
N	636	635	637	634	
Person-years	3369	3360	3329	3361	
<u>Type 2 diabetes</u>					
n	24	30	24	35	
Incidence (/10^4 py)	74.0	93.3	73.7	111.5	
IRR (model 1)	1.00	1.54	1.55	1.97	0.004
	(reference)	(0.97, 2.46)	(0.94, 2.54)	(1.27, 3.10)	
IRR (model 2)	1.00	1.31	1.27	1.64	0.043
	(reference)	(0.82, 2.10)	(0.77, 2.09)	(1.05, 2.59)	
<u>Diabetes medication</u>					
n	17	21	21	26	
Incidence (/10^4 py)	52.3	64.3	64.3	82.0	
IRR (model 1)	1.00	1.51	1.92	2.06	0.005
	(reference)	(0.87, 2.66)	(1.10, 3.38)	(1.23, 3.54)	
IRR (model 2)	1.00	1.26	1.49	1.67	0.048
	(reference)	(0.72, 2.22)	(0.85, 2.64)	(0.99, 2.87)	

Incidence rates weighted for loss to follow-up. Ratio estimations from Poisson regression models, weighted for loss to follow-up. Model 1 adjusted for age and sex, model 2 additionally adjusted for BMI. P trend calculated entering PTFQI quartile as a continuous variable.

PTFQI: Parametric Thyroid Feedback Quantile-based Index; n/N: number of new cases/number at risk; IRR: Incidence Rate Ratio.

Table 3: Incidence of type 2 diabetes and related conditions across pituitary set-points for the thyroid axis measured with PTFQI (abnormal HbA1c excluded at baseline).

	PTFQI quartiles				
	1st	**2nd**	**3rd**	**4th**	**p trend**
	[min.,-0.19)	**[-0.19,0.00)**	**[0.00,0.22)**	**[0.22,max.]**	
N	615	622	622	619	
Person-years	3262	3289	3253	3277	
Type 2 diabetes					
n	16	22	17	27	
Incidence (/10^4 py)	50.4	68.4	52.5	86.7	
IRR (model 1)	1.00	1.72	1.63	2.48	0.002
	(reference)	(0.99, 3.05)	(0.89, 2.98)	(1.46, 4.30)	
IRR (model 2)	1.00	1.46	1.33	2.13	0.009
	(reference)	(0.84, 2.60)	(0.72, 2.44)	(1.26, 3.71)	
Diabetes medication					
n	9	14	14	19	
Incidence (/10^4 py)	28.0	41.9	42.9	60.5	
IRR (model 1)	1.00	1.95	2.44	3.12	<0.001
	(reference)	(0.94, 4.18)	(1.18, 5.23)	(1.60, 6.46)	
IRR (model 2)	1.00	1.60	1.87	2.63	0.005
	(reference)	(0.77, 3.44)	(0.89, 4.05)	(1.34, 5.47)	

Incidence rates weighted for loss to follow-up. Ratio estimations from Poisson regression models, weighted for loss to follow-up. Model 1 adjusted for age and sex, model 2 additionally adjusted for BMI. P trend calculated entering PTFQI quartile as a continuous variable.

PTFQI: Parametric Thyroid Feedback Quantile-based Index; n/N: number of new cases/number at risk; IRR: Incidence Rate Ratio.

This table is similar to Table 2, but excluding abnormal HbA1c at baseline.

Figures

Figure 1. Scatterplot of thyrotropin (TSH) vs free thyroxine (fT4) and Barplot of crude type 2 diabetes incidence rates across intervals of parametric thyroid feedback quantile-based index (PTFQI) in the SHIP sample (N=2542)

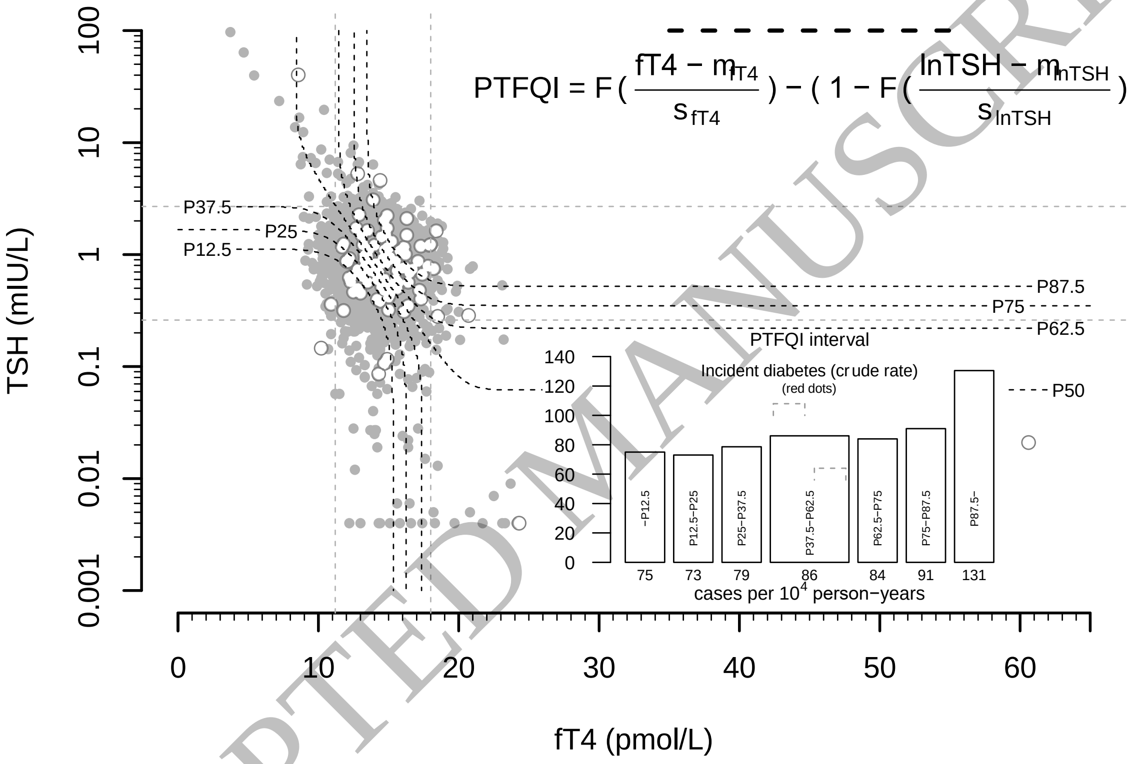

Figure 2. Type 2 diabetes incidence rate ratios of one unit increase of parametric thyroid feedback quantile-based index (PTFQI) across obesity strata