Life expectancy is unaffected by thyroid function parameters in euthyroid subjects

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Letter to the Editor

Life expectancy is unaffected by thyroid function parameters in euthyroid subjects: The PREVEND cohort study

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During the past few years the concept is emerging that differences in thyroid function status even within the reference range may impact on a wide number of health issues [1,2]. Low-normal thyroid function, as reflected by higher thyroid stimulating hormone (TSH) and/or lower free thyroxine (FT_4) or free triiodothyronine (FT_3) levels within the euthyroid reference range, associate with enhanced atherosclerosis susceptibility [2]. A high-normal TSH level within the reference range was associated with mortality from cardiovascular diseases (CVD) in a single cohort study, but such a relationship was not found in a recent meta-analysis [3]. High-normal TSH and low-normal FT_4 levels may also predict incident type 2 diabetes mellitus (T2DM) [4]. On the other hand, low-normal thyroid function attenuates the risk of stroke [5], whereas a higher FT_4 level within the euthyroid range was related to the risk of sudden cardiac death [6]. Higher FT_4 levels may associate with the occurrence of solid malignancy also after exclusion of thyroid function altering medication [7]. Given the complex and partly opposing associations of thyroid function status with such major and prevalent morbidities, it is clinically relevant to discern whether thyroid hormone levels affect life expectancy. We initiated the present prospective analysis to determine the extent to which TSH, FT_4 and FT_3 levels are associated with alterations in life expectancy.

We studied a random subset of participants of the Prevention of Renal and Vascular End Stage Disease (PREVEND) cohort, aged 28–75 years, living in the city of Groningen, The Netherlands [8]. The local medical ethical committee of the University of Groningen, The Netherlands, approved the study. All participants gave written informed consent. For the current study, we excluded subjects not being euthyroid (defined as a TSH, an FT_4 and an FT_3 level within their respective reference range), subjects with a thyroid disorder, using thyroid hormones, anti-thyroid drugs, amiodarone or lithium carbonate at the baseline evaluation (1996 to 1998). Information on medication use was combined with information from a pharmacy-dispensing registry. Applying these selection criteria 2431 subjects were eligible for the current analyses. Demographic variables, previous CVD, metabolic syndrome and T2DM categorization, and laboratory data were obtained as described [8]. The participants were studied after an overnight fast. Sera were stored at − 80 °C until analyses. Serum TSH (Architect; Abbott Laboratories, Abbott Park, IL, USA; reference range 0.35–4.94 mU/L), FT_4 (AxSYM; Abbott Laboratories; reference range 9.14–23.81 pmol/L) and FT_3 (AxSYM; Abbott Laboratories; reference range; 2.23–5.35 pmol/L) were measured by microparticle enzyme immunoassays. Anti-thyroid peroxidase (anti-TPO) autoantibodies were determined using an automated enzyme-linked immunoassay (Abbott Laboratories; kit number 5F57; positive at ≥ 12 kU/L).

Follow-up time was defined as the period between the baseline evaluation and death, loss to follow-up or the end of follow up time (01-01-2011), whichever came first. Data on mortality were obtained from the municipal register, and the cause of death was obtained by linking the number of the death certificate to the primary cause of death as coded by the Central Bureau of Statistics using the International Classification of Diseases. The Ninth Revision (ICD-9) was used for coding data until 01-01-2009; after this date, data were coded according to the Tenth Revision (ICD-10).

Data analysis was performed using IBM SPSS software (version 23.0, SPSS Inc. Chicago, IL, USA) and Microsoft Excel 2010 for Windows. Life expectancy was calculated as described in detail elsewhere [9,10]. In brief, the median life expectancy of all individual participants was derived from the annual sex-specific mortality reports from the Netherlands, as provided by the Dutch Central Office of Statistics (http://www.CBS.nl). The starting point was defined as the date of blood collection of each individual. To adjust for differences in age, survival times were adjusted for the median life expectancy of individuals in the general population with the same age and sex [9,10]. The time basis used in the adjusted graphs is negative life expectancy ("Minus EXPECTANCY", in years). Differences were tested using the log-rank test with left and right censoring, and median life expectancy as time base [10]. Two-sided *P*-values < 0.05 were considered significant.

2431 subjects (age 46.0 ± 11.8 years; 50.8% women) were included. At the end of a median follow-up time of 13.0 [interquartile range 12.6–13.1] years, 218 (9%) subjects had died: 62 (28.4%) from CVD, 88 (40.4%) from malignancy and 68 (31.2%) from other causes. Demographic and laboratory data in subjects who died vs. subjects who were still alive are shown in Supplemental Table 1. TSH, FT_4 and FT_3 values, and anti-TPO autoantibody status were similar in subjects who had deceased compared to subjects who were alive at the end of follow-up.

After adjusting for age, sex and birth cohort the study population was subdivided based on TSH, FT_4 and FT_3 levels. The upper tertile of TSH was compared with its lower two tertiles, whereas the lower tertile of FT_4 and FT_3 were compared with their upper two tertiles (Fig. 1a–c). At the start of the study, no difference in life expectancy was present between subjects having a TSH level in the upper tertile vs. subjects in the lower two tertiles

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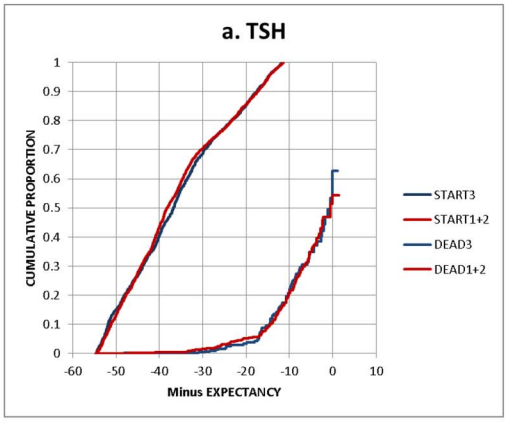
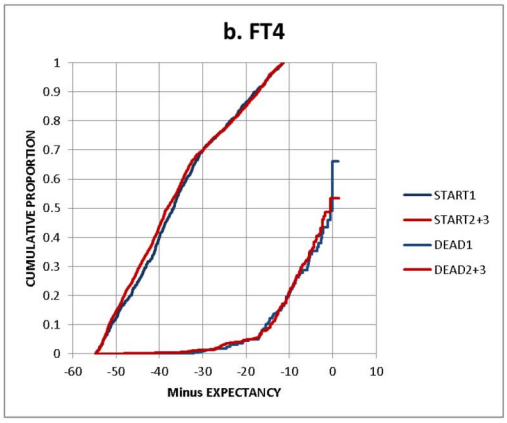
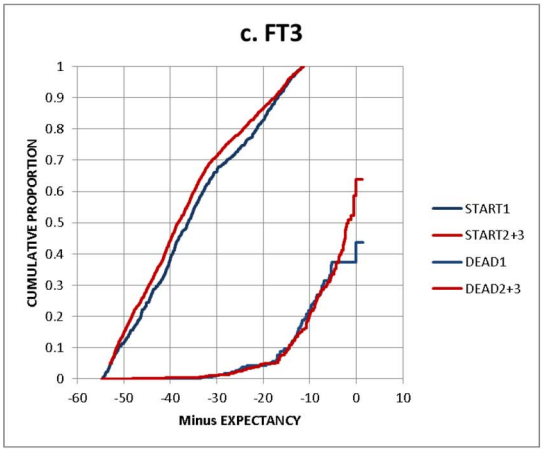

a. TSH
CUMULATIVE PROPORTION
Minus EXPECTANCY
START3
START1+2
DEAD3
DEAD1+2


b. FT4
CUMULATIVE PROPORTION
Minus EXPECTANCY
START1
START2+3
DEAD1
DEAD2+3


c. FT3
CUMULATIVE PROPORTION
Minus EXPECTANCY
START1
START2+3
DEAD1
DEAD2+3

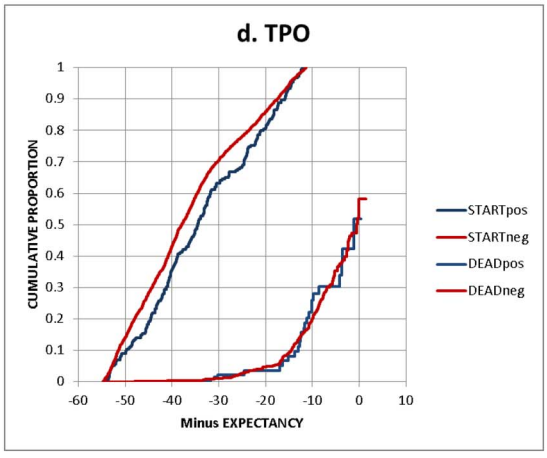

d. TPO
CUMULATIVE PROPORTION
Minus EXPECTANCY
STARTpos
STARTneg
DEADpos
DEADneg

Fig. 1. a–d. Kaplan-Meier estimates of overall survival, adjusted for sex, age and birth cohort. The time base (X-axis) represents the minus life expectancy (Minus EXPECTANCY) in years. The lines at the left part show the distribution of the life expectancy at the start of the study, i.e. the date of blood sampling. The lines at the right part of the diagram show the distribution of the life expectancy at death. The blue lines show the life expectancy of patients in the upper tertile of a. TSH and the lowest tertile of b. FT_4 and c. FT_3. The red lines show the life expectancy of patients at the lower two tertiles combined of a. TSH, and the upper two tertiles of b. FT_4 and c. FT_3. Panel d shows the life expectancy in subjects being positive (blue lines) and negative (red lines) for anti-thyroid peroxidase (anti-TPO) autoantibodies. Life expectancy at the start of the study is also not significantly different for TSH and FT_4, but was different for FT_3 ($P < 0.001$) and anti-TPO autoantibody status ($P = 0.046$). This indicates that subjects with lower FT_3 values were older as were subjects being positive for anti-TPO autoantibodies. No significant differences in life expectancy at death were observed (all $P > 0.60$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

($P = 0.52$), and between subjects with FT_4 values in the lower tertile vs. the upper two tertiles ($P = 0.14$). Likewise, no age difference was found between the subjects with TSH in the upper compared to the lower two tertiles ($P = 0.42$), and between the subjects with lower FT_4 values compared to the upper two tertiles ($P = 0.21$). Subjects having FT_3 values in the lower tertile were older than subjects in the upper two tertiles ($P = 0.001$), and had a shorter life expectancy at the start of the study ($P = 0.002$). No differences in life expectancy at the end of follow-up between the upper and the lower two tertiles were observed for TSH (Fig. 1a, $P = 0.92$), nor between the lower tertile vs. the upper two tertiles of FT_4 (Fig. 1b, $P = 0.76$) and FT_3 (Fig. 1c, $P = 0.61$). Subjects with positive anti-TPO autoantibodies were older ($P = 0.046$) and had a lower life expectancy at the start of the study (Fig. 1d, $P = 0.002$). Life expectancy at the end of follow-up did not differ between according to anti-TPO autoantibodies status ((Fig. 1d, $P = 0.81$). Life expectancy did not vary according to thyroid function in men and women separately ($P \geq 0.31$ for all comparisons; data not shown). Anti-TPO antibody status also did not significantly affect life expectancy in men ($P = 0.07$), and women ($P = 0.66$) separately. In subsidiary analyses stratifying for MetS (n = 465) or T2DM (n = 72) at baseline, life expectancy was not affected by to thyroid function status or the presence of anti-TPO antibodies ($P \geq 0.60$ for all comparisons; data not shown).

Apparently opposing effects of thyroid function status on major health problems make it elusive to predict any association of thyroid function status with survival beforehand. This population-based study is the first to show that neither TSH, nor FT_4 or FT_3 levels did significantly impact on life expectancy. We observed no influence of anti-TPO autoantibody status on survival. Assessment of life expectancy is increasingly used to evaluate the overall effect of a certain condition on survival. The method that we employed makes use of the annual sex-specific mortality reports in the Netherlands, and has been proved informative in previous analyses with respect other morbidities [9,10]. We divided our cohort according to the upper vs. the lower two tertiles of TSH, and conversely according to the lower vs. the upper two tertiles of FT_4 and FT_3. This approach was chosen to determine the possible influence of low-normal thyroid function status as determined by either higher TSH or lower FT_4 and FT_3 levels on life expectancy. In the interpretation of our results, it is important that each individual probably has a narrow set-point of thyroid function status [2], justifying the use of a single set of thyroid function measurements at baseline as potential determinants of life expectancy. We cannot exclude, however, that this approach may have resulted in some underestimation of the relationship of thyroid function status with outcome.

The strength of the associations of thyroid function status with a number of cardiovascular biomarkers was suggested to be enhanced in the context of hyperglycemia [2]. Furthermore, low-normal thyroid function is probably associated with a higher prevalence of MetS [2,8]. Nonetheless, neither thyroid function nor anti-TPO autoantibody status was associated with altered life expectancy in subjects with MetS and T2DM separately.

Our study was carried out in a large, well-characterized population with a considerable follow-up period and comprehensive measurement of thyroid function parameters. The frequency of mortality causes appeared to be unremarkable, suggesting that the population studied was representative of the north of the Netherlands. Anti-TPO antibodies were more frequently positive in older individuals. Since anti-TPO status predicts future development of (subclinical) hypothyroidism, we included this variable in our analysis. Notably, age effects on thyroid function variables were eliminated to affect our prospective life expectancy analysis since we adjusted survival times for the median life expectancy of individuals in the general population with the same age and sex [9,10]. Finally, PREVEND participants are predominantly white, making it uncertain whether the present findings also pertain to other ethnicities.

In conclusion, this large population-based cohort study demonstrates that differences in thyroid function status within the euthyroid reference range, measured at a single time point, do not have a major impact on life expectancy.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2017.10.017.

Conflict to interest

The authors declare that there is no conflict of interest.

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References

[1] Taylor PN, Razvi S, Pearce SH, Dayan CM. Clinical review: a review of the clinical consequences of variation in thyroid function within the reference range. J Clin Endocrinol Metab 2013;98:3562–71.
[2] Tienhoven-Wind van, Dullaart RP. Low-normal thyroid function and novel cardiometabolic biomarkers. Nutrients 2015;16(7):1352–77.
[3] Åsvold BO, Vatten LJ, Bjøro T, Bauer DC, Bremner A, Cappola AR, et al. Thyroid function within the normal range and risk of coronary heart disease: an individual participant data analysis of 14 cohorts. JAMA Intern Med 2015;175:1037–47.
[4] Chaker L, Ligthart S, Korevaar TI, Hofman A, Franco OH, Peeters RP, et al. Thyroid function and risk of type 2 diabetes: a population-based prospective cohort study. BMC Med 2016;14(1):150.
[5] Chaker L, Baumgartner C, den Elzen WP, Collet TH, Ikram MA, Blum MR, et al. Thyroid function within the reference range and the risk of stroke: an individual participant data analysis. J Clin Endocrinol Metab 2016;101:4270–82.
[6] Chaker L, van den Berg ME, Niemeijer MN, Franco OH, Dehghan A, Hofman A, et al. Thyroid function and sudden cardiac death: a prospective population-based cohort study. Circulation 2016;134:713–22.
[7] Khan SR, Chaker L, Ruiter R, Aerts JG, Hofman A, Dehghan A, et al. Thyroid function and cancer risk: the Rotterdam study. J Clin Endocrinol Metab 2016;101:5030–6.
[8] Roos A, Bakker SJ, Links TP, Gans RO, Wolffenbuttel BH. Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. J Clin Endocrinol Metab

2007;92:491–6.
[9] Links TP, van Tol KM, Jager PL, Plukker JT, Piers DA, Boezen HM, et al. Life expectancy in differentiated thyroid cancer: a novel approach to survival analysis. Endocr Relat Cancer 2005;12:273–80.
[10] van Dijk D, Plukker JT, van der Horst-Schrivers AN, Jansen L, Brouwers AH, Muller-Kobold A, et al. The value of detectable thyroglobulin in patients with differentiated thyroid cancer after initial ^{131}I therapy. Clin Endocrinol (Oxf) 2011;74:104–10.

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