# Defining Optimal Health Range for Thyroid Function Based on the Risk of Cardiovascular Disease

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**Context:** Reference ranges of thyroid-stimulating hormone (TSH) and free thyroxine ($FT_4$) are defined by their distribution in apparently healthy populations (2.5th and 97.5th percentiles), irrespective of disease risk, and are used as cutoffs for defining and clinically managing thyroid dysfunction.

**Objective:** To provide proof of concept in defining optimal health ranges of thyroid function based on cardiovascular disease (CVD) mortality risk.

**Design and Participants:** In all, 9233 participants from the Rotterdam Study (mean age, 65.0 years) were followed up (median, 8.8 years) from baseline to date of death or end of follow-up period (2012), whichever came first (689 cases of CVD mortality).

**Main Outcomes:** We calculated 10-year absolute risks of CVD mortality (defined according to the SCORE project) using a Fine and Gray competing risk model per percentiles of TSH and $FT_4$, modeled nonlinearly and with sex and age adjustments.

**Results:** Overall, $FT_4$ level >90th percentile was associated with a predicted 10-year CVD mortality risk >7.5% ($P = 0.005$). In men, $FT_4$ level >97th percentile was associated with a risk of 10.8% ($P < 0.001$). In participants aged ≥65 years, absolute risk estimates were <10.0% below the 30th percentile (~14.5 pmol/L or 1.10 ng/dL) and ≥15.0% above the 97th percentile of $FT_4$ (~22 pmol/L or 1.70 ng/dL).

**Conclusions:** We describe absolute 10-year CVD mortality risks according to thyroid function (TSH and $FT_4$) and suggest that optimal health ranges for thyroid function can be defined according to disease risk and are possibly sex and age dependent. These results need to be replicated with sufficient samples and representative populations. **(*J Clin Endocrinol Metab* 102: 2853–2861, 2017)**

Reference ranges for blood and other clinical tests are predominantly statistically defined using the 2.5th and 97.5th percentile interval of the distribution in an apparently healthy population. These reference ranges are typically established under the assumption of a normal distribution or a log-normal distribution and are

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Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; $FT_4$, free thyroxine; TSH, thyroid-stimulating hormone.

therefore also referred to as "normal ranges." This definition of the reference range does not account for whether individuals are symptomatic or at risk for potential adverse events or disease. Nevertheless, these biochemically defined reference values are frequently used to define sickness and health in clinical practice, ignoring the inherent risks of the population.

The reference ranges for thyroid function tests, defined by thyroid-stimulating hormone (TSH) and free thyroxine ($FT_4$), are examples of reference ranges defined by their distribution. TSH and $FT_4$ reference ranges are currently used as cutoffs to define subclinical and overt thyroid disease and guide treatment decisions. However, accumulating evidence suggests that subclinical thyroid dysfunction, defined by TSH outside the reference range but $FT_4$ within the reference range, is also associated with various clinical adverse outcomes, including coronary heart disease (CHD) and cardiovascular mortality at the extremes (1, 2). Moreover, even differences in thyroid function within the defined reference range are associated with differing risk of cardiovascular events, including atrial fibrillation, stroke, sudden cardiac death, and cardiovascular mortality (3–7). On the basis of the increased risk of CHD in subclinical hypothyroidism, current guidelines advocate treatment with levothyroxine above a TSH level of 10 mIU/L, independent of $FT_4$ value (8). Extending this concept, the reevaluation of thyroid function ranges could take clinical adverse events into account and thus move from reference ranges toward "optimal health ranges" for thyroid function.

This approach has been successfully applied to management of myocardial infarction, stroke, and diabetes using cholesterol, blood pressure, and glucose measurements (9). For example, the defined range for total cholesterol level does not rely on the distribution of total cholesterol in a specific population, but rather on the associated 10-year risk of cardiovascular mortality (9). Pursuing the same strategy for thyroid function might not be as straightforward as for other biomarkers, however. The risk of adverse events is relevant for both high and low thyroid function, suggesting a nonlinear association; this contrasts with cholesterol level, where the focus is on the high end of the measurement. Furthermore, thyroid dysfunction is not associated solely with cardiovascular disease (CVD) but has important implications for bone health and possibly cognitive health (10–13).

We therefore aimed to calculate the 10-year absolute risk of cardiovascular mortality in a large population-based cohort study using the two most common parameters of thyroid function, TSH and $FT_4$. We further aimed to define optimal health ranges according to provided absolute risk estimates in the whole cohort as well as by sex and age groups.

## Subjects and Methods

### The Rotterdam Study

The Rotterdam Study is a prospective, population-based cohort study investigating the determinants and occurrence of age-related diseases in middle-aged and elderly populations in Rotterdam, the Netherlands. The aims and design of the Rotterdam Study have been described in detail elsewhere (14). The Rotterdam Study consists of three independent cohorts: Rotterdam Study Cohort 1, including 7983 participants aged ≥55 years (baseline, 1990 to 1993); Rotterdam Study Cohort 2, including 3011 participants aged ≥55 years (baseline 2000 to 2001); and Rotterdam Study Cohort 3, including 3932 participants aged ≥45 years (baseline 2006 to 2008). The Rotterdam Study was approved by the medical ethics committee according to the Population Screening Act: Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands.

### Study population

We selected data from participants from the third visit of the first cohort (1997 to 1999; n = 4797) and the first visits of the second (2000 to 2001; n = 3011) and third (2006 to 2008; n = 3932) cohorts if TSH or $FT_4$ measurements were performed and they were not using thyroid function−altering medication, including levothyroxine, antithyroid drugs, amiodarone, or corticosteroids. We did not use the first visit of the first cohort because thyroid function was measured with a different assay. All participants in the present analysis provided written informed consent to participate and for acquisition of information from their treating physician. All study participants were followed up from the day of baseline laboratory testing to the date of death or end of the follow-up period, 1 January 2012, whichever came first.

### Assessment of thyroid function and other baseline measurements

TSH and $FT_4$ measurements were performed using the same methods and assay in blood samples collected between 1997 and 2008, depending on the cohort, and were stored at −80°C (electrochemiluminescence immunoassay for $FT_4$ and thyrotropin; Roche). Body mass index was calculated as body mass (kg) divided by the square of body height (m). Serum cholesterol was measured using standard laboratory techniques. Systolic blood pressure was calculated as the average of two consecutive measurements. More than 95% of participants were in a fasting state when blood was drawn (morning) at the Rotterdam Study center visit. Information on tobacco smoking was derived from baseline questionnaires. Information on medication use was obtained from questionnaires in combination with pharmacy records.

### Outcome definition

We selected CVD as the primary outcome of interest because it is a leading burden of disease, morbidity, and mortality (15). In addition, the association of subclinical and overt thyroid dysfunction with CVD mortality is well established (1). Secondary outcomes of interest were CHD and stroke (fatal and nonfatal). Methods for collection of data and outcome definitions have been previously described (14, 16, 17).

Information on the vital status of all participants was obtained on a weekly basis from the central registry of the municipality in Rotterdam and through digital linkage with records from general practitioners working in the study area. The cause of death was established by abstracting information from the medical records of the general practitioners or nursing home physicians and hospital discharge letters. Cardiovascular mortality was defined according to the SCORE project definition of fatal CVD, including the International Classification of Diseases-10 codes I10-25, I44-51, I61-73, and R96 (9, 18). To test the robustness of our findings, we repeated the absolute risk estimate calculations using the definition of CVD mortality previously published by the Rotterdam Study, which also included nonatherosclerotic cardiovascular mortality (16). CHD was defined as myocardial infarction, cardiac revascularization procedure, or CHD mortality. Stroke was defined according to World Health Organization criteria as a syndrome of rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than vascular origin, including ischemic or hemorrhagic strokes. Outcomes were adjudicated by a committee that was blinded to laboratory results.

### *Statistical analyses*

Absolute values of TSH and especially $FT_4$ are assay dependent, but the different immunoassays of TSH or $FT_4$ correlate well in nonpregnant adult populations (19, 20), as previously also shown in the Rotterdam Study (21). Therefore, to enhance the generalizability of our results, we analyzed the association of TSH or $FT_4$ (in percentiles) with the outcomes defined later. Absolute 10-year risk estimates of CVD mortality used the percentiles of TSH and $FT_4$ and were calculated according to the Fine and Gray model, taking the competing risk of non-CVD deaths into account, and were adjusted for age and sex (22). The competing risk for the CHD and stroke analyses were non-CHD and nonstroke deaths, respectively. In addition, we performed predefined analyses stratifying by age categories and sex. We performed sensitivity analyses using a Rotterdam Study–based definition for CVD mortality (16), additionally adjusting the TSH analyses for $FT_4$ and *vice versa*, as well as additionally adjusting the analyses for cardiovascular risk factors used in the SCORE project charts (*i.e.*, smoking, systolic blood pressure level, and cholesterol level) (9). We used the following cutoffs for the risk estimates and color denomination of risk categories, which were slightly adjusted from the SCORE project because of the higher average age in our population: low risk (<2.0%, white), low-intermediate risk (2.0% to 5.0%, light gray), intermediate risk (5.0% to 7.5%, gray), high-intermediate risk (7.5% to 10.0%, dark gray), and high risk (≥10.0%, black).

For the CHD analyses, we excluded all participants with prevalent or missing information on CHD at baseline (n = 685). For the stroke analyses, we excluded all participants with missing information at baseline or a history of stroke (n = 319). We performed a goodness-of-fit test for the Fine and Gray model for the absolute risk estimations using the Zou Laird Fine test, and this revealed no linear, quadratic, or log time-varying effects of TSH or $FT_4$ ($P > 0.1$ for all analyses). Linearity of absolute risk estimates was tested with restricted cubic splines with three knots at the 10th, 50th, and 90th percentiles. Analyses were performed in R [survival, rms, crrSC, and cmprsk packages *R*-project, version 3.0.2; Institute for Statistics and Mathematics, R Core Team (2013), Vienna, Austria].

## Results

We included 9233 participants with a mean age of 65.0 years (standard deviation, 9.8 years), of whom 55.9% were female (Table 1). During an average follow-up of 8.8 years, with a total of 75,981 person-years, 2166 deaths occurred, of which 689 were CVD deaths according to the SCORE criteria and 692 were CVD deaths according to the Rotterdam Study criteria. There were 642 CHD events and 553 stroke events during follow-up. Completeness of follow-up was 99.6% (23).

### Absolute risk estimates of cardiovascular mortality

Ten-year absolute risk estimates for CVD mortality across the range of TSH and $FT_4$ values are plotted in Fig. 1. CVD mortality increased with higher $FT_4$ levels ($P = 0.005$) and lower TSH levels, although it was not statistically significant for the latter. The best fit for both TSH and $FT_4$ analyses was nonlinear ($P$ value for nonlinearity $< 0.001$) (Fig. 1).

Table 2 shows the different percentile cutoffs of TSH and $FT_4$ values with the predicted absolute 10-year risk estimates based on nonlinear association. Overall, $FT_4$ values above the 97th percentile (absolute level of ~22 pmol/L or 1.7 ng/dL) were associated with a predicted 10-year risk of 9.6% ($P = 0.005$). $FT_4$ levels above the 90th percentile corresponded to an increased risk of 7.5% and were higher for CVD mortality (absolute level of ~19 pmol/L or 1.5 ng/dL). Sensitivity analyses additionally adjusted for cardiovascular risk factors using the Rotterdam

**Table 1. Baseline Characteristics of Rotterdam Study Participants With TSH or $FT_4$ Measurements and No Thyroid Function–Altering Medication**

| Variable | Mean (SD)[a] |
|---|---|
| Number of participants | 9233 |
| Age, y | 65.0 (9.8) |
| Female, n (%) | 5157 (55.9) |
| History of diabetes, n (%) | 1097 (11.9) |
| BMI, kg/m$^2$ | 27.2 (4.2) |
| Cholesterol, mmol/L | 5.7 (1.0) |
| Smoking, n (%) | |
| Current | 1975 (21.4) |
| Past | 4380 (47.4) |
| Never | 2878 (31.2) |
| Systolic BP, mm Hg | 139.5 (21.0) |
| TSH, mIU/L, median (IQR) | 1.90 (1.29–2.74) |
| $FT_4$, pmol/L | 15.6 (2.2) |
| $FT_4$, ng/dL | 1.21 (0.2) |

Abbreviations: BMI, body-mass index; BP, blood pressure; IQR, interquartile range; n, number; SD, standard deviation.

[a]Values are mean (SD) unless otherwise specified.

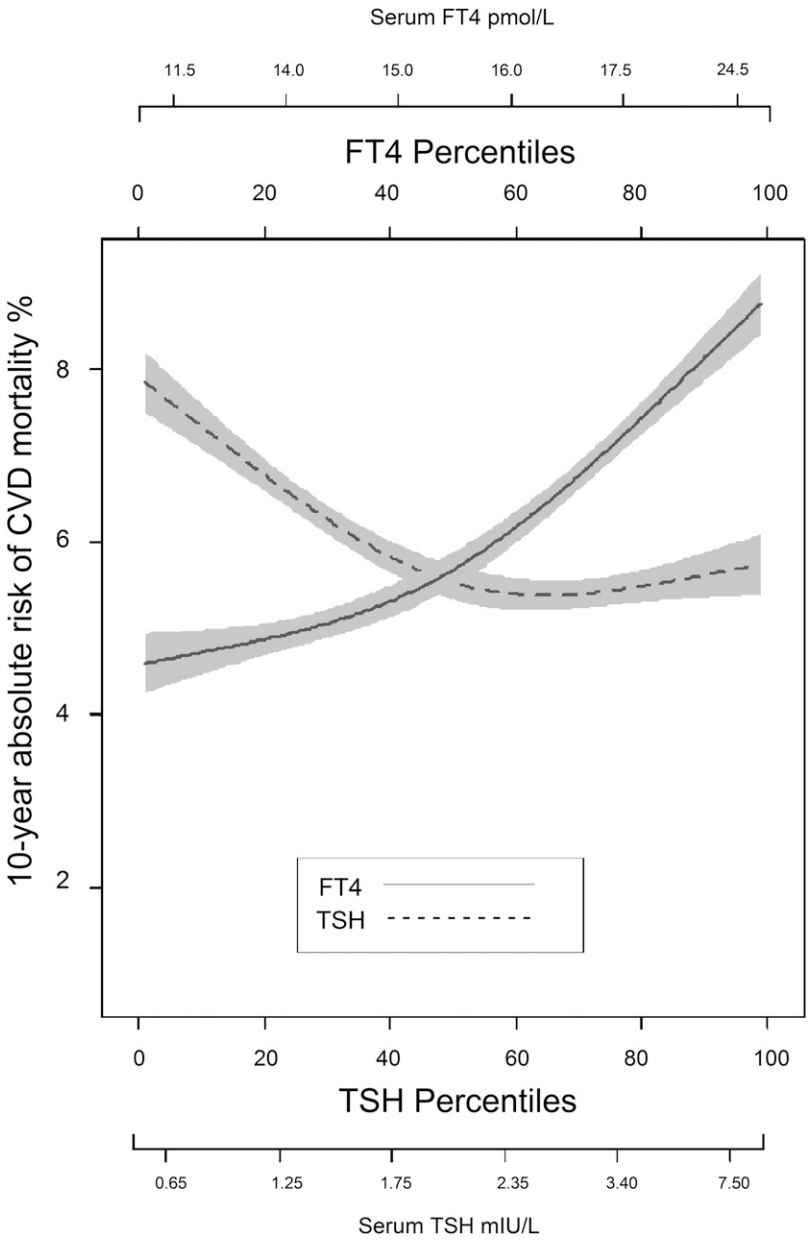


**Figure 1.** Absolute 10-year risk of CVD mortality by TSH and $FT_4$ levels. Absolute 10-year risks of CVD mortality were calculated by taking competing risk of death by other causes into account and were plotted against TSH and $FT_4$ percentiles and absolute values, with 95% confidence intervals. *P* value for nonlinearity is <0.001 for both TSH and $FT_4$ analyses.

Study definition of CVD mortality or adjusting the TSH analyses for $FT_4$ and *vice versa*, did not change the definition of the cutoffs meaningfully (Supplemental Table 1). TSH levels were inversely associated with CVD mortality but were not statistically significant (Table 1).

For men, a risk of ≥10.0% occurred at the 97th percentile of $FT_4$ values ($P < 0.001$) and a risk of ≥7.5% occurred at the 60th percentile (Table 3). In women, there was no association of thyroid function markers with risk of CVD mortality (Table 3). In participants younger than 65 years, the risk of CVD mortality increased with decreasing TSH levels ($P = 0.009$), with a risk of ≥2.0% at the 30th percentile and lower (~1.40 mIU/L), whereas $FT_4$ levels were not associated with CVD mortality (Table 4). In participants older than 65 years (Table 4), the absolute risk estimates were <10.0% below the 30th percentile and ≥15.0% above the 97th percentile of $FT_4$.

### Absolute risk estimates of CHD and stroke

Supplemental Fig. 1 plots the absolute risk estimates of CHD and stroke against the continuous $FT_4$ and TSH levels. In the Fine and Gray models, the association of TSH or $FT_4$ with CHD events was not statistically significant ($P > 0.5$). Higher $FT_4$ levels were associated with an increased risk of stroke ($P = 0.009$). TSH levels were inversely associated with the risk of stroke, but this did not reach statistical significance. The best fit for the CHD analyses was linear, whereas the best fit for the stroke analyses was nonlinear (*P* value for nonlinearity < 0.001) (Supplemental Fig. 1).

## Discussion

In this study, we propose reference ranges of TSH and $FT_4$ that are based on disease risk (*i.e.*, absolute risk estimates of CVD) as proof of concept. On the basis of our findings, the proposed upper limit for $FT_4$ could be the 90th percentile, independent of TSH level. The optimal health ranges for thyroid function based on CVD seem to differ between men and women, and the associations were not statistically significant in women. In participants older than 65 years, the absolute risk estimates of CVD were <10.0% below the 30th percentile (~14.5 pmol/L or 1.1 ng/dL) and ≥15.0% above the 97th percentile of $FT_4$ (~22 pmol/L or 1.7 ng/dL). The associations of TSH and $FT_4$ with CVD mortality were nonlinear. The association of thyroid function with stroke followed a similar pattern, but the association with CHD showed a linear association.

Reference ranges for the thyroid function biomarkers TSH and $FT_4$ have been derived statistically mainly from the 2.5th and 97.5th percentiles, similar to reference

**Table 2. Absolute 10-Year Risk Estimates for CVD Mortality According to Percentiles of TSH and $FT_4$ (n = 9227)[a]**

| | Predicted 10-Year Absolute Risk of Event (n = 689 Cases) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **TSH, Percentile** | **<2nd** | **2th–5th** | **5th–10th** | **10th–20th** | **20th–30th** | **30th–40th** | **40th–50th** | **50th–60th** | **60th–70th** | **70th–80th** | **80th–90th** | **90th–95th** | **95th–97th** | **>97th** | ***P* Trend** |
| Absolute risk estimates | 8.3% | 8.3% | 7.4% | 6.9% | 6.5% | 5.9% | 6.0% | 5.5% | 5.5% | 5.4% | 5.3% | 6.0% | 5.5% | 6.0% | 0.59 |
| n | 149 | 164 | 471 | 944 | 959 | 952 | 930 | 958 | 944 | 953 | 933 | 444 | 257 | 169 | |
| Mean TSH | 0.03 | 0.19 | 0.53 | 0.97 | 1.26 | 1.52 | 1.76 | 2.04 | 2.36 | 2.77 | 3.45 | 4.54 | 5.74 | 13.53 | |
| **$FT_4$, Percentile** | **<2nd** | **2th–5th** | **5th–10th** | **10th–20th** | **20th–30th** | **30th–40th** | **40th–50th** | **50th–60th** | **60th–70th** | **70th–80th** | **80th–90th** | **90th–95th** | **95th–97th** | **>97th** | ***P* Trend** |
| Absolute risk estimates | 4.5% | 4.4% | 5.1% | 4.7% | 4.7% | 5.2% | 5.8% | 6.0% | 6.2% | 6.9% | 7.5% | 8.4% | 8.9% | 9.6% | 0.005 |
| n | 185 | 190 | 476 | 941 | 952 | 961 | 940 | 953 | 939 | 947 | 911 | 463 | 238 | 131 | |
| Mean $FT_4$ pmol/L | 8.93 | 11.57 | 12.57 | 13.46 | 14.16 | 14.73 | 15.27 | 15.80 | 16.36 | 17.01 | 17.83 | 18.85 | 19.82 | 22.01 | |
| Mean $FT_4$ ng/dL | 0.69 | 0.90 | 1.00 | 1.05 | 1.10 | 1.14 | 1.19 | 1.23 | 1.27 | 1.32 | 1.39 | 1.46 | 1.54 | 1.71 | |

Models were adjusted for age and sex and were computed using a competing risk model. Risk legend: low risk (<2.0%, white), low-intermediate risk (2.0%–5.0%, light gray), intermediate (5.0%–7.5%, gray), high-intermediate risk (7.5%–10.0%, dark gray), and high risk (≥ 10.0%, black).

[a]Six people were excluded because of missing cause of death.

ranges of other laboratory results and clinical tests (24–26). Subclinical and overt thyroid disease is subsequently defined by these biochemical and statistical reference ranges, which, in general, do not take future health and disease risks into account. However, some guidelines do uphold additional cutoffs for treatment on the basis of studies showing an increased risk of CVD at certain levels (8, 27). For example, the European Thyroid Association guidelines on subclinical hypothyroidism (8) makes a distinct separation between TSH levels below and above 10 mIU/L for consideration of levothyroxine treatment. These recommendations are based on a study by the Thyroid Studies Collaboration that provided evidence for a higher relative risk of CHD with TSH levels >10 mIU/L (1). However, to our knowledge, no studies specifically addressed optimal health ranges based on absolute risk estimates of adverse health outcomes.

Overall, our study showed an absolute 10-year risk of 7.5% or higher with $FT_4$ levels above the 90th percentile, corresponding to an $FT_4$ cutoff level of approximately

**Table 3. Absolute 10-Year Risk Estimates for CVD Mortality According to Percentiles of TSH and $FT_4$ (n= 9227)[a]**

| | Predicted 10-Year Absolute Risk of Event (n = 689) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Men, N = 4072; Cases = 357** | | | | | | | | | | | | | | |
| **TSH, Percentile** | **<2nd** | **2th–5th** | **5th–10th** | **10th–20th** | **20th–30th** | **30th–40th** | **40th–50th** | **50th–60th** | **60th–70th** | **70th–80th** | **80th–90th** | **90th–95th** | **95th–97th** | **>97th** | ***P* Trend** |
| Absolute risk estimates | 11.4% | 8.6% | 8.8% | 8.0% | 7.1% | 7.0% | 7.3% | 6.4% | 6.6% | 6.4% | 6.4% | 7.8% | 7.2% | 7.1% | 0.46 |
| n | 44 | 78 | 216 | 461 | 461 | 472 | 452 | 450 | 408 | 418 | 354 | 159 | 60 | 39 | |
| **$FT_4$, Percentile** | **<2nd** | **2th–5th** | **5th–10th** | **10th–20th** | **20th–30th** | **30th–40th** | **40th–50th** | **50th–60th** | **60th–70th** | **70th–80th** | **80th–90th** | **90th–95th** | **95th–97th** | **>97th** | ***P* Trend** |
| Absolute risk estimates | 4.4% | 5.3% | 6.1% | 5.4% | 5.5% | 6.1% | 6.8% | 7.5% | 7.6% | 8.3% | 8.4% | 9.0% | 9.0% | 10.8% | <0.001 |
| n | 62 | 51 | 199 | 377 | 352 | 412 | 393 | 450 | 425 | 461 | 458 | 244 | 128 | 60 | |
| | **Women, N = 5155; Cases = 332** | | | | | | | | | | | | | | |
| **TSH, Percentile** | **<2nd** | **2th–5th** | **5th–10th** | **10th–20th** | **20th–30th** | **30th–40th** | **40th–50th** | **50th–60th** | **60th–70th** | **70th–80th** | **80th–90th** | **90th–95th** | **95th–97th** | **>97th** | ***P* Trend** |
| Absolute risk estimates | 7.0% | 8.1% | 6.3% | 5.9% | 5.9% | 4.7% | 4.6% | 4.7% | 4.6% | 4.5% | 4.6% | 5.0% | 5.1% | 5.9% | 0.99 |
| n | 105 | 86 | 255 | 483 | 498 | 480 | 478 | 508 | 536 | 535 | 579 | 285 | 197 | 130 | |
| **$FT_4$, Percentile** | **<2nd** | **2th–5th** | **5th–10th** | **10th–20th** | **20th–30th** | **30th–40th** | **40th–50th** | **50th–60th** | **60th–70th** | **70th–80th** | **80th–90th** | **90th–95th** | **95th–97th** | **>97th** | ***P* Trend** |
| Absolute risk estimates | 4.8% | 4.3% | 4.2% | 4.2% | 4.3% | 4.5% | 5.0% | 4.7% | 5.1% | 5.6% | 6.7% | 7.8% | 8.8% | 8.6% | 0.27 |
| n | 123 | 139 | 277 | 564 | 600 | 549 | 547 | 503 | 514 | 486 | 453 | 219 | 110 | 71 | |

Models were adjusted for age and sex and were computed using a competing risk model. Risk legend: low risk (<2.0%, white), low-intermediate risk (2.0%–5.0%, light gray), intermediate (5.0%–7.5%, gray), high-intermediate risk (7.5%–10.0%, dark gray), and high risk (≥10.0%, black).

[a]Six people were excluded because of missing cause of death.

**Table 4. Absolute 10-Year Risk Estimates for CVD Mortality According to Percentiles of TSH and $FT_4$ (n = 9227)[a]**

| Predicted 10-Year Absolute Risk of Event (n = 689) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Age <65 y, N= 5172; Cases = 82** | | | | | | | | | | | | | | | |
| **TSH, Percentile** | **<2nd** | **2th–5th** | **5th–10th** | **10th–20th** | **20th–30th** | **30th–40th** | **40th–50th** | **50th–60th** | **60th–70th** | **70th–80th** | **80th–90th** | **90th–95th** | **95th–97th** | **>97th** | ***P* Trend** |
| Absolute risk estimates | 2.6% | 3.0% | 2.6% | 2.4% | 2.2% | 1.9% | 1.7% | 1.4% | 1.3% | 1.2% | 1.0% | 0.9% | 0.8% | 0.9% | 0.009 |
| n | 56 | 59 | 234 | 490 | 523 | 557 | 532 | 573 | 564 | 580 | 554 | 233 | 134 | 83 | |
| **$FT_4$, Percentile** | **<2nd** | **2th–5th** | **5th–10th** | **10th–20th** | **20th–30th** | **30th–40th** | **40th–50th** | **50th–60th** | **60th–70th** | **70th–80th** | **80th–90th** | **90th–95th** | **95th–97th** | **>97th** | ***P* Trend** |
| Absolute risk estimates | 1.2% | 1.1% | 1.3% | 1.3% | 1.3% | 1.5% | 1.5% | 1.8% | 1.8% | 1.9% | 2.1% | 2.2% | 2.4% | 2.4% | 0.20 |
| n | 96 | 97 | 285 | 565 | 556 | 561 | 516 | 526 | 508 | 535 | 512 | 239 | 115 | 61 | |
| **Age ≥65 y, N = 4055, Cases = 607** | | | | | | | | | | | | | | | |
| **TSH, Percentile** | **<2nd** | **2th–5th** | **5th–10th** | **10th–20th** | **20th–30th** | **30th–40th** | **40th–50th** | **50th–60th** | **60th–70th** | **70th–80th** | **80th–90th** | **90th–95th** | **95th–97th** | **>97th** | ***P* Trend** |
| Absolute risk estimates | 11.8% | 11.5% | 12.2% | 11.9% | 11.5% | 11.3% | 11.2% | 11.1% | 11.1% | 11.2% | 10.9% | 11.4% | 10.5% | 10.8% | 0.76 |
| n | 93 | 105 | 237 | 454 | 436 | 395 | 398 | 385 | 380 | 373 | 379 | 211 | 123 | 86 | |
| **$FT_4$ percentile** | **<2nd** | **2th–5th** | **5th–10th** | **10th–20th** | **20th–30th** | **30th–40th** | **40th–50th** | **50th–60th** | **60th–70th** | **70th–80th** | **80th–90th** | **90th–95th** | **95th–97th** | **>97th** | ***P* Trend** |
| Absolute risk estimates | 8.1% | 7.9% | 10.2% | 9.3% | 9.2% | 10.2% | 10.7% | 11.1% | 11.4% | 13.1% | 14.1% | 14.7% | 14.9% | 15.7% | 0.005 |
| n | 89 | 93 | 191 | 376 | 396 | 400 | 424 | 427 | 431 | 412 | 399 | 224 | 123 | 70 | |

Models were adjusted for age and sex and were computed using a competing risk model. Risk legend: low risk (<2.0%, white), low-intermediate risk (2.0%–5.0%, light gray), intermediate (5.0%–7.5%, gray), high-intermediate risk (7.5%–10.0%, dark gray), abd high risk (≥ 10.0%, black).

[a]Six people were excluded because of missing cause of death.

19 pmol/L (~1.5 ng/dL). However, this differs in participants younger than 65 years compared with those older than 65 years. Also, there seems to be a differential association of thyroid function with absolute risk of CVD when men are compared with women. This can be attributed, at least partially, to the difference in background absolute risks between the two sexes in our study, which showed that women have an inherently lower risk of CVD. Aside from background risk of CVD, however, there also appears to be a thyroid-dependent differential risk when comparing men with women, which may be explained by a difference in set points between the sexes (28). These findings need to be confirmed and validated across different populations, but they could suggest that a sex-specific reference range is needed.

In our study, higher $FT_4$ levels were associated with an increased risk of CVD mortality, whereas TSH levels showed an expected opposite relation with CVD mortality that did not reach statistical significance. The current study is not the first to report an association of $FT_4$ with clinical events, whereas the association is lower or absent with TSH (3, 6, 21). On the basis of the log-linear relationship between TSH and $FT_4$, TSH is thought to be the most sensitive marker in subjects with thyroid disease. The lack of association with TSH is therefore remarkable. One explanation could be that in euthyroid subjects, TSH predominantly reflects the pituitary-thyroid axis set point rather than disease risk (29), whereas independent of TSH, circulating $FT_4$ (and subsequently free triiodothyronine acting intracellularly) represents the bioavailable thyroid hormone that can be taken up by cells, thereby leading to clinical consequences of thyroid hormones peripherally.

Cholesterol is a modifiable risk factor for CVD mortality, and diagnosis and treatment targets for cholesterol are included within optimal primary and secondary prevention of CVD mortality. Our study showed that $FT_4$ is also a potentially modifiable risk factor for CVD and CVD mortality, especially in men and the elderly. For cholesterol, the SCORE risk chart for low-risk countries (9) describes the average risk difference for 65-year-old men with a cholesterol level of 7 mmol/L compared with 65-year-old men with a cholesterol level of 4 mmol/L as ~4.0%. This is similar to the risk difference between men with an average age of 65 years in the highest 10th percentile of $FT_4$ (cutoff ~1.5 ng/dL) and those in the lowest 10th percentile (cutoff ~1.0 ng/dL), namely 4.3%. Whether modification of higher $FT_4$ levels with antithyroid drugs will result in this cardiovascular mortality risk reduction needs to be determined.

Our study has several strengths, including the population-based design, the large study population, the completeness of follow-up, and the fact that outcomes were defined independently from baseline thyroid function. Nevertheless, the currently proposed optimal health

ranges should be interpreted with caution. First, although CVD is one of the most important clinical outcomes, the presented absolute risk estimates were based solely on cardiovascular mortality, and as such, our findings should be considered as proof of concept. Furthermore, the Netherlands is classified by the European Society of Cardiology as a country with a low cardiovascular mortality risk; therefore, estimates are not generalizable to countries with a higher CVD mortality risk (30). The Rotterdam Study consisted of participants aged 45 years and older who were mainly Caucasians with, on average, sufficient iodine status (31, 32). Also, only one baseline measurement of thyroid function was available, which holds true for most population-based cohort studies. The intraindividual set point was much tighter than the interindividual set point, meaning that within an individual, changes in time were much smaller than changes between individuals (33). Nevertheless, we could not investigate how changes in thyroid function could affect CVD risk and whether repeated measurements of thyroid function could better differentiate risk among cohort participants.

The absolute levels of TSH and especially $FT_4$ depend on the assay used and are therefore variable. Immunoassays for $FT_4$ are affected by changes in serum-binding proteins that occur in disease and pregnancy (34). We therefore used the percentiles of the measurements to study the associations and define optimal health ranges because of the strong correlation between the different assays of TSH or $FT_4$ in community-dwelling nonpregnant populations. These results are therefore potentially more generalizable to other populations. This is also the reason to advice that the calculation of these percentiles is country, iodine status, region, and if possible even laboratory specific.

The previously mentioned limitations of our study also highlight the need for further research. Therefore, our approach to defining thyroid function adequacy, which focused on cardiovascular mortality, needs to be confirmed in similar populations and replicated in complementary populations, such as younger participants and other ethnicities, and in regions with different current and historical iodine status (35).

CVD is an established and well-studied outcome in relation to thyroid function. However, there is increasing interest in the association of thyroid function with other outcomes as well, such as cognition. Therefore, consensus is needed on which clinical outcomes beyond CVD are or could be relevant in defining optimal health ranges for thyroid function. Finally, beyond the discussion of optimal health ranges for thyroid function, consensus is needed on which cardiovascular risk is considered too high and whether this is similar for all populations. For example, a 10-year absolute risk of 2.5% for CVD mortality for a 45-year-old person might not be deemed equally acceptable compared to the same risk in a 75-year-old person.

This was a population-based study, and therefore risks and benefits of treatment decisions were not explored. Although randomized controlled trials provide the best evidence for defining treatment cutoffs, they are costly and do not always address the timeliest issues. In the absence of results from such trials in the near future, defining optimal health ranges by determining the absolute risk estimates of disease in observational studies of representative populations is perhaps most feasible.

In summary, we propose defining thyroid function on the basis of not only population distribution but also health and disease risk. We described the absolute 10-year risk of cardiovascular mortality associated with TSH and $FT_4$ and provided an example of defining optimal health ranges according to cardiovascular mortality risk using data from a large population-based study. Further research is needed to investigate optimal health ranges based on thyroid-relevant clinical outcomes in sufficiently powered studies with representative samples from multiple populations.

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