Supplementary Online Content

Bano A, Dhana K, Chaker L, et al. Association of thyroid function with life expectancy with and without cardiovascular disease: the Rotterdam Study. *JAMA Intern Med*. Published online September 18, 2017. doi:10.1001/jamainternmed.2017.4836

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

Study population

Baseline measurements for our study were performed during the third visit of the first cohort (1997-1999, n=4797) and the first visit of the second (2000-2001, n=3011) and third (2006-2008, n=3932) cohorts of the Rotterdam Study. The original cohort during these three visits included a total of 11 740 participants, of which 10 050 had available blood measurements. Thyroid function measurements were performed in a random sample of 9702 participants. Of these, we excluded 16 participants without complete follow-up data, 1346 with TSH or FT4 outside the normal reference ranges and 555 with past thyroid disease or taking thyroid medications. The remaining 7785 participants were eligible for the analysis **(eFigure)**. Follow-up started at the date of thyroid function assessment.

Covariates

The baseline home interview provided information on medical history, medication use, tobacco smoking, alcohol consumption, education level and marital status.[1] Smoking habits were categorized as current, former and never smoking. Education level was divided into four categories: elementary, lower secondary, higher secondary and tertiary education, in accordance with the standard international classification of education.[2] Marital status was categorized as single, married, widowed and divorced/separated. Serum glucose and lipid levels were measured by an automated enzymatic procedure (Mannheim System). Anthropometric measurements were performed in the research center by trained medical staff. Body mass index was calculated as weight in kilograms divided by

height in meters squared. Blood pressure was measured in the sitting position on the right arm and calculated as the mean of two measurements using a random-zero sphygmomanometer. Diabetes mellitus was defined as fasting serum glucose level of 7 mmol/L or more, non-fasting plasma glucose level of 11.1 mmol/L or more (when fasting samples were absent) or the use of antidiabetic medication.[1]

eTable 1. HRs of incident CVD and death among TSH and FT4 tertiles, excluding the first 2 years of follow-up for CVD and death						
			TSH		**FT4**	
Transition	**Cases/PY**	**TSH/FT4 tertiles**	**Model 1 HR (95% CI)**	**Model 2 HR (95% CI)**	**Model 1 HR (95% CI)**	**Model 2 HR (95% CI)**
Incident CVD	610/38139	Tertile 1	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
		Tertile 2	0.83 (0.69; 1.01)	0.84 (0.69; 1.02)	1.14 (0.94; 1.40)	1.14 (0.93; 1.40)
		Tertile 3	0.95 (0.79; 1.16)	0.96 (0.79; 1.17)	**1.25 (1.02; 1.53)**	**1.24 (1.02; 1.52)**
Mortality among those without CVD	639/39950	Tertile 1	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
		Tertile 2	**0.78 (0.65; 0.94)**	**0.80 (0.67; 0.96)**	1.21 (0.98; 1.47)	1.19 (0.97; 1.46)
		Tertile 3	**0.72 (0.60; 0.88)**	**0.77 (0.63; 0.94)**	**1.43 (1.18; 1.74)**	**1.35 (1.11; 1.65)**
Mortality among those with CVD	425/7753	Tertile 1	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
		Tertile 2	0.98 (0.78; 1.23)	0.92 (0.73; 1.16)	1.29 (1.00; 1.67)	**1.31 (1.01; 1.68)**
		Tertile 3	**0.77 (0.61; 0.98)**	**0.76 (0.60; 0.97)**	**1.49 (1.17; 1.89)**	**1.49 (1.17; 1.90)**

Model 1: age, sex and cohort.
Model 2: Model 1, smoking, alcohol intake, education level, marital status, diabetes mellitus, body mass index, systolic blood pressure, total cholesterol, triglycerides, usage of antihypertensive and lipid-lowering medications.
Abbreviations: HR, hazard ratio; CVD, cardiovascular disease; TSH, thyroid-stimulating hormone; FT4, free thyroxine; PY, person-years; CI, confidence interval.

eTable 2. HRs for incident CVD and death among TSH and FT4 tertiles, excluding users of thyroid function-altering medications and additionally adjusting for prevalent cancer

			TSH	FT4
Transition	**Cases/PY**	**TSH/FT4 tertiles**	**HR (95% CI)**	**HR (95% CI)**
Incident CVD	763/37814	Tertile 1	1 (Reference)	1 (Reference)
		Tertile 2	0.87 (0.73; 1.03)	1.14 (0.95; 1.37)
		Tertile 3	0.94 (0.78; 1.12)	**1.32 (1.10; 1.57)**
Mortality among those without CVD	771/40460	Tertile 1	1 (Reference)	1 (Reference)
		Tertile 2	**0.78 (0.65; 0.91)**	1.16 (0.96; 1.39)
		Tertile 3	**0.76 (0.64; 0.91)**	**1.43 (1.20; 1.72)**
Mortality among those with CVD	524/8445	Tertile 1	1 (Reference)	1 (Reference)
		Tertile 2	0.93 (0.76; 1.15)	1.24 (0.98; 1.56)
		Tertile 3	**0.80 (0.65; 1.00)**	**1.57 (1.26; 1.94)**

Hazard ratios are adjusted for age, sex, cohort, smoking, alcohol intake, education level, marital status, diabetes mellitus, body mass index, systolic blood pressure, total cholesterol, triglycerides, usage of antihypertensive and lipid-lowering medications and prevalent cancer.

Abbreviations: HR, hazard ratio; CVD, cardiovascular disease; TSH, thyroid-stimulating hormone; FT4, free thyroxine; PY, person-years; CI, confidence interval.

eTable 3. LE at age 50 years, among TSH and FT4 tertiles, in men and women over 8 years of follow-up*

	Total LE	Dif total LE	Dif LE free of CVD	Dif LE with CVD
TSH tertiles				
Men				
Tertile 1	29.6	Ref	Ref	Ref
Tertile 2	32.3	2.7	1.4	1.3
Tertile 3	31.5	2.0	1.3	0.6
Women				
Tertile 1	34.6	Ref	Ref	Ref
Tertile 2	36.3	1.7	3.1	-1.3
Tertile 3	36.2	1.6	1.4	0.2
FT4 tertiles				
Men				
Tertile 1	31.8	Ref	Ref	Ref
Tertile 2	30.5	-1.2	-0.9	-0.3
Tertile 3	28.8	-3.0	-2.8	-0.2
Women				
Tertile 1	37.9	Ref	Ref	Ref
Tertile 2	35.8	-2.1	-1.5	-0.6
Tertile 3	33.9	-4.0	-2.7	-1.3

*Data are given as years. Differences are calculated using the first tertile as reference.
All LEs have been calculated with hazard ratios adjusted for age, cohort, smoking, alcohol intake, education level, marital status, diabetes mellitus, body mass index, systolic blood pressure, total cholesterol, triglycerides, usage of antihypertensive and lipid-lowering medications.
Abbreviations: LE, life expectancy; TSH, thyroid-stimulating hormone; FT4, free thyroxine; Dif, difference; CVD, cardiovascular disease; Ref, reference.

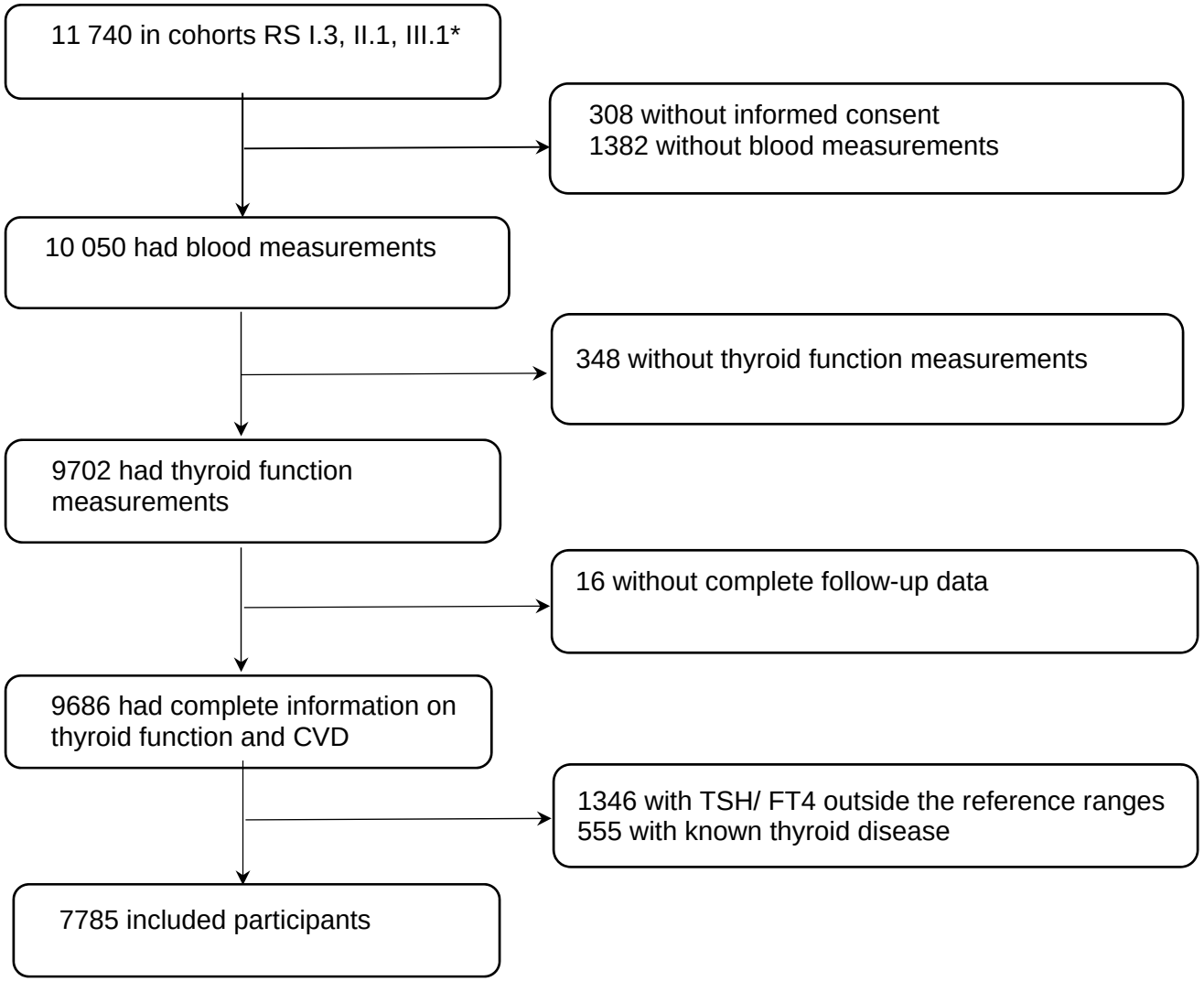
eTable 4. LE at age 50 years, among thyroid status categories, in men and women*					
	TN	**Total LE**	**Dif total LE**	**Dif LE free of CVD**	**Dif LE with CVD**
Men					
Euthyroidism	3667	**31.0 (30.8; 31.3)**	Ref	Ref	Ref
Hypothyroidism†	245	**31.3 (29.5; 32.9)**	0.3 (-1.7; 1.9)	0.1 (-2.4; 2.5)	0.2 (-1.5; 2.1)
Hyperthyroidism†	80	**29.6 (26.6; 32.9)**	-1.4 (-4.4; 2.0)	-3.7 (-7.6; 0.1)	2.3 (-1.3; 6.4)
Women					
Euthyroidism	4028	**35.6 (35.3; 35.9)**	Ref	Ref	Ref
Hypothyroidism†	551	**36.7 (35.5; 37.8)**	1.1 (-0.4; 2.3)	0.8 (-0.7; 2.2)	0.3 (-0.8; 1.3)
Hyperthyrodism†	110	**36.0 (33.7; 38.4)**	0.4 (-2.1; 2.9)	**2.3 (0.2; 4.4)**	**-1.9 (-3.1;-0.4)**

*For this analysis, we included participants without known thyroid disease and not using thyroid function-altering medications (i.e. thyroid medications, amiodarone, corticosteroids). Differences are calculated using the euthyroid category as reference. Data are given as years (95% confidence intervals). All LEs have been calculated with hazard ratios adjusted for age, cohort, smoking, alcohol intake, education level, marital status, diabetes mellitus, body mass index, systolic blood pressure, total cholesterol, triglycerides, usage of antihypertensive and lipid-lowering medications.

†Includes subclinical and clinical range.

Abbreviations: LE, life expectancy; TN, total number; Dif, difference; CVD, cardiovascular disease; Ref, reference.

eFigure. Flow chart for the selection of study participants



*A total of 11740 participants were enrolled during the third visit of the first cohort ($n = 4797$) and the first visit of the second ($n = 3011$) and third ($n = 3932$) cohorts of The Rotterdam Study

Abbreviations: CVD, cardiovascular disease

eReferences

1. Hofman A, Brusselle GG, Darwish Murad S, et al. The Rotterdam Study: 2016 objectives and design update. *Eur J Epidemiol.* 2015;30(8):661-708.

2. Unesco. International Standard Classification of Education. November 2007.