Thyroid Antibody Status, Subclinical Hypothyroidism, and the Risk of Coronary Heart Disease: An Individual Participant Data Analysis

Tinh-Hai Collet, Douglas C. Bauer, Anne R. Cappola, Bjørn O. Åsvold, Stefan Weiler, Eric Vittinghoff, Jacobijn Gussekloo, Alexandra Bremner, Wendy P. J. den Elzen, Rui M. B. Maciel, Mark P. J. Vanderpump, Jacques Cornuz, Marcus Dörr, Henri Wallaschofski, Anne B. Newman, José A. Sgarbi, Salman Razvi, Henry Völzke, John P. Walsh, Drahomir Aujesky, and Nicolas Rodondi* for the Thyroid Studies Collaboration

Context: Subclinical hypothyroidism has been associated with increased risk of coronary heart disease (CHD), particularly with thyrotropin levels of 10.0 mIU/L or greater. The measurement of thyroid antibodies helps predict the progression to overt hypothyroidism, but it is unclear whether thyroid autoimmunity independently affects CHD risk.

Objective: The objective of the study was to compare the CHD risk of subclinical hypothyroidism with and without thyroid peroxidase antibodies (TPOAbs).

Data Sources and Study Selection: A MEDLINE and EMBASE search from 1950 to 2011 was conducted for prospective cohorts, reporting baseline thyroid function, antibodies, and CHD outcomes.

Data Extraction: Individual data of 38 274 participants from six cohorts for CHD mortality followed up for 460 333 person-years and 33 394 participants from four cohorts for CHD events.

Data Synthesis: Among 38 274 adults (median age 55 y, 63% women), 1691 (4.4%) had subclinical hypothyroidism, of whom 775 (45.8%) had positive TPOAbs. During follow-up, 1436 participants died of CHD and 3285 had CHD events. Compared with euthyroid individuals, age- and gender-adjusted risks of CHD mortality in subclinical hypothyroidism were similar among individuals with and without TPOAbs [hazard ratio (HR) 1.15, 95% confidence interval (CI) 0.87–1.53 vs HR 1.26, CI 1.01–1.58, *P* for interaction = .62], as were risks of CHD events (HR 1.16, CI 0.87–1.56 vs HR 1.26, CI 1.02–1.56, *P* for interaction = .65). Risks of CHD mortality and events increased with higher thyrotropin, but within each stratum, risks did not differ by TPOAb status.

Conclusions: CHD risk associated with subclinical hypothyroidism did not differ by TPOAb status, suggesting that biomarkers of thyroid autoimmunity do not add independent prognostic information for CHD outcomes. (***J Clin Endocrinol Metab*** **99: 3353–3362, 2014)**

The prevalence of subclinical hypothyroidism increases with age and is highest among older women (1, 2). Controversy persists as to whether population-wide screening and treatment of subclinical thyroid dysfunction are warranted (1, 3). Current evidence about the risks of subclinical hypothyroidism remains limited (1, 3), and randomized clinical trials on relevant clinical outcomes have not been performed to date (1, 4). Our recent individual participant data analysis found that subclinical hypothyroidism [defined as elevated TSH level (4.5–19.9 mIU/L) and normal free T_4 level] was associated with coronary heart disease (CHD) mortality and CHD events, with a stronger association for those with TSH of 10.0 mIU/L or greater (5).

The presence of thyroid antibodies predicts the risk of progression from subclinical to overt hypothyroidism (6–

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

Received January 28, 2014. Accepted May 15, 2014.
First Published Online June 10, 2014

* Author affiliations are shown at the bottom of the next page.

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; HF, heart failure; HR, hazard ratio; HUNT, Nord-Trøndelag Health Study; MI, myocardial infarction; TgAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody.

9). Among 1877 subjects (56% women), both raised TSH level, and the presence of thyroid antibodies at baseline were associated with development of hypothyroidism over a 20-year follow-up (6). Among 92 women (mean age 50.7 y) with subclinical hypothyroidism followed up for 9 years, the incidence of overt hypothyroidism increased from 23.2% to 58.5% with the presence of antimicrosomal antibodies ($P = .03$) (10). Although recommendations in guidelines about measuring thyroid antibodies to better identify patients who should receive levothyroxine replacement differ (1, 3), physicians include thyroid antibody status in their decision of whether to treat subclinical hypothyroidism (11).

Because the presence of thyroid antibodies is associated with more progression from subclinical to overt hypothyroidism (6–10) and overt hypothyroidism with increased cardiovascular risk (12), one may infer that subclinical hypothyroidism with positive thyroid antibodies might be also associated with increased risks of CHD mortality or events, although this has not been studied in appropriately sized studies with clinical outcomes. Indeed, thyroid antibodies have been associated with increased markers of endothelial dysfunction that may lead to atherosclerosis (13). However, it is unknown whether the presence of thyroid antibodies in subclinical hypothyroidism predicts patient-relevant cardiovascular outcomes, such as CHD events. Only a few previous studies have reported clinical cardiovascular outcomes, with conflicting data (14–18). The studies also had limited power with a relatively low number of events and did not provide subgroup analyses (eg, by TSH levels or age).

We therefore aimed to compare the risks of CHD mortality and events associated with subclinical hypothyroidism by thyroid antibody status using individual participant data from our Thyroid Studies Collaboration (5, 19, 20).

Materials and Methods

Data sources and study selection

As previously described (5, 19, 20), we identified prospective cohort studies and collected their individual participant data based on a systematic literature review of MEDLINE and EMBASE databases from 1950 to June 30, 2011, with no language restriction, and screened bibliographies of selected articles (Supplemental Appendix Methods). We included studies with a priori criteria: full-text published longitudinal cohort studies, reporting baseline levels of thyroid function (TSH and T_4) and antibodies, with a control euthyroid group and prospective follow-up of cause-specific mortality and CHD outcomes. We excluded studies in which only participants taking thyroid medications (antithyroid drugs, levothyroxin, or amiodarone) or participants with only overt hypothyroidism (high TSH and low T_4 levels) were included.

Data extraction and quality assessment

Investigators from each original study were invited to join the Thyroid Studies Collaboration and to share individual participant data, as previously described (5, 19, 20). We collected demographic data, TSH, free T_4, or total T_4 in one study (14), thyroid antibodies, baseline cardiovascular risk factors (ie, blood pressure, cigarette smoking status, total cholesterol level, diabetes mellitus), body mass index (BMI) (weight in kilograms divided by squared height in meters), cardiovascular and thyroid medication use, and outcome data on CHD events and mortality. We assessed study quality using previous criteria (21) after collecting additional information from study authors: methods of outcome adjudication and ascertainment, accounting for confounders, and completeness of follow-up.

Data synthesis and analysis

Similar to our previous analyses (5, 19, 20), we used a uniform TSH cutoff level, based on an expert consensus meeting of our Thyroid Studies Collaboration (International Thyroid Conference, Paris, 2010), expert reviews (1), and previous large cohorts (15, 22). Euthyroidism was defined as TSH 0.45–4.49 mIU/L and subclinical hypothyroidism as TSH 4.5–19.9 mIU/L and normal T_4 level. Similar to our previous analysis on subclinical hypothyroidism (5), we used a study-specific TSH reference range of 6.0–21.5 mIU/L for participants in the Whickham Survey (14) because of the first-generation TSH RIA in this study that gives higher measured TSH values than current assays (23). For participants in the Study of Health in Pomerania (24), an iodine fortification program was started a few years before inclusion; thus, a TSH reference range of 0.25–2.12 mIU/L was used as suggested for iodine-deficient areas (25); we further performed a sensitivity analysis excluding this study. Without this study-specific TSH range, a large group of participants would have been considered subclinically hyperthyroid (n = 706, 18.4%) and very few subclinically hypothyroid (n = 13, 0.4%).

Service of Endocrinology, Diabetes, and Metabolism (T.-H.C.), University Hospital of 1011 Lausanne, Switzerland; Department of Ambulatory Care and Community Medicine (T.-H.C., J.C.), University of Lausanne, 1011 Lausanne, Switzerland; Departments of Epidemiology and Biostatistics (D.C.B., E.V.) and Medicine (D.C.B.), University of California, San Francisco, San Francisco, California 94143; Division of Endocrinology, Diabetes, and Metabolism (A.R.C.), Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104; Department of Public Health (B.O.Å.), Norwegian University of Science and Technology, N-7491 Trondheim, Norway; Department of Endocrinology (B.O.Å.), St Olavs Hospital, Trondheim University Hospital, N-7006 Trondheim, Norway; Department of General Internal Medicine (S.W., D.A., N.R.), Inselspital, University of Bern, 3000 Bern, Switzerland; Department of Clinical Pharmacology and Toxicology (S.W.), University Hospital of Zürich, 8091 Zürich, Switzerland; Department of Public Health and Primary Care (J.G., W.P.J.d.E.), Leiden University Medical Center, 2300 RC Leiden, The Netherlands; School of Population Health (A.B.) and School of Medicine and Pharmacology (J.P.W.), The University of Western Australia, Crawley, and Department of Endocrinology and Diabetes (J.P.W.), Sir Charles Gairdner Hospital, Nedlands, Western Australia 6009, Australia; Division of Endocrinology (R.M.B.M., J.A.S.), Department of Medicine, Federal University of Sao Paulo, 04023-900 São Paulo, Brazil; Department of Endocrinology (M.P.J.V.), Royal Free Hospital, London NW3 2PF, United Kingdom; Clinic for Internal Medicine B (M.D.) and Institute of Clinical Chemistry and Laboratory Medicine (H.W.), University Medicine Greifswald, and Institute for Community Medicine (H.V.), Study of Health in Pomerania/Clinical-Epidemiological Research, University of Greifswald, D-17487 Greifswald, Germany; DZHK (German Centre for Cardiovascular Research) (M.D., H.W.), partner site Greifswald, Germany; Department of Epidemiology (A.B.N.), University of Pittsburgh, Pittsburgh, Pennsylvania 15260; Division of Endocrinology (J.A.S.), Faculdade de Medicina de Marília, 17519-030 Marília, Brazil; and Department of Endocrinology (S.R.), Gateshead Health Foundation National Health Service Trust, Gateshead NE9 6SX, United Kingdom

For T_4 level, we used study- and method-specific cutoff values (Supplemental Appendix Table 1) because this measurement shows a greater intermethod variation than TSH assays. Eight participants among the 1691 with TSH 4.5–19.9 mIU/L had missing T_4 values (Supplemental Appendix Table 1): seven of these participants had TSH values ranging from 4.6 to 6.4 mIU/L and one a TSH of 15 mIU/L. As previously performed (5, 19, 20), we assumed that these participants had subclinical hypothyroidism because most adults with this degree of TSH elevation have subclinical rather than overt hypothyroidism (2). We performed a sensitivity analysis excluding those participants with missing T_4 values.

Thyroid antibodies were measured by different assays in the original cohorts, and we used assay-specific cutoff values (Supplemental Appendix Table 1). In two older cohorts, levels of antimicrosomal antibodies (22) and thyroid anticytoplasmic antibodies (14) were available instead of the more precise thyroid peroxidase antibodies (TPOAbs) in the four other cohorts (26). Therefore, we conducted a sensitivity analysis excluding the two studies relying on older assays for thyroid antibodies. We also performed sensitivity analyses excluding thyroid medication users at baseline and then at baseline and during follow-up as well as analyses limited to participants with a TSH of 10.0 mIU/L or greater.

Outcomes were CHD events and CHD mortality. Similar to our previous analyses (5, 19), we used more homogenous definitions to limit the outcome heterogeneity observed in a previous study-level analysis (21). Similar to the Framingham risk score (27), we limited cardiovascular mortality to CHD mortality or sudden death (Supplemental Appendix Table 1). We defined CHD events as nonfatal myocardial infarction (MI) or CHD death [equivalent to hard events in the Framingham risk score (27)] or hospitalization for angina or coronary revascularization (22). Data on heart failure (HF) outcome were available from one study (22) with thyroid antibodies. Incident HF events were assessed in participants free of HF at baseline and adjudicated every 6 months based on an interview, a review of medical records, and other support documents without the knowledge of thyroid status (28).

Statistical analyses

Similar to our previous studies (5, 19, 20), we analyzed the association between subclinical hypothyroidism with and without antibodies and each outcome using separate Cox proportional hazard models of individual participant data from each cohort (SAS version 9.2; SAS Institute Inc; Stata 12.1; StataCorp). Pooled estimates for each outcome were calculated with random-effects models based on the inverse variance model as recommended in two-stage individual participant data analyses (29, 30). Results were summarized using forest plots (Review Manager version 5.1.7; Nordic Cochrane Centre). To assess heterogeneity across studies, we applied the I^2 statistic, which measures the inconsistency across studies attributable to heterogeneity instead of chance alone (31). We analyzed the potential additional effect of TPOAbs to predict CHD outcomes in subclinical hypothyroidism by interaction tests: we compared pooled estimates of the risk of CHD outcomes for TPOAb-positive subclinical hypothyroidism vs euthyroidism and TPOAb-negative subclinical hypothyroidism vs euthyroidism using interaction tests.

Primary analyses were adjusted for age and sex [some traditional cardiovascular risk factors being potential mediators of CHD risk associated with subclinical hypothyroidism (12)] and then further adjusted for cardiovascular risk factors (systolic blood pressure, smoking status, total cholesterol, diabetes), BMI, and lipid-lowering and antihypertensive medications. To explore the potential sources of heterogeneity, we performed predefined subgroup and sensitivity analyses as in our previous analyses (5, 19, 20). We conducted stratified analyses by age, sex, and TSH category representing them as aggregate forest plots to summarize our findings. For some strata with participants but no event in subgroup analyses, we used penalized likelihood methods (32) to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). We checked the proportional hazard assumption using graphical methods and the Schoenfeld test (33). To assess potential publication bias, we used age- and sex-adjusted funnel plots and the Egger test (34).

Results

We identified reports of six prospective cohorts meeting all inclusion criteria (Supplemental Appendix Figure 1) comprising 38 274 adults (median age 55 y, 62.9% women) recruited from the general population. A total of 36 583 were euthyroid and 1691 (4.4%) had subclinical hypothyroidism, of whom 775 (45.8%) had positive TPOAbs (Table 1). Median follow-up was 12.2 years (interquartile range 11.2–13.1 y) for a total of 460 333 person-years, with a loss to follow-up rate less than 5% in all included studies.

During follow-up, 1436 participants in the whole sample died of CHD (Table 2), and 3285 CHD events occurred among 33 394 participants from four cohorts having data on CHD events (14–16, 22) (Table 3). In age- and sex-adjusted analyses compared with euthyroid individuals, risks of CHD mortality were similar among those with TPOAb-positive subclinical hypothyroidism (HR 1.15, CI 0.87–1.53) and those with TPOAb-negative subclinical hypothyroidism (HR 1.26, CI 1.01–1.58, *P* for interaction = .62) (Supplemental Appendix Figure 2). The risks of CHD events were also similar between subclinically hypothyroid TPOAb-positive and -negative individuals (HR 1.16, CI 0.87–1.56 vs HR 1.26, CI 1.02–1.56, respectively, *P* for interaction = .65) (Supplemental Appendix Figure 2). Because heterogeneity was present across studies for CHD events (I^2 = 49%) but not for CHD mortality (I^2 = 0%), we subsequently assessed potential differences of risks according to subgroups. In stratified analyses, risks for CHD mortality and events increased with higher TSH levels, although with limited statistical evidence for a trend; power was more limited for these subgroup analyses compared with our previous analyses with 11 cohorts (5). However, at each TSH level, risks did not differ by TPOAb status (Figure 1). Risks differed slightly

Table 1. Baseline Characteristics of Individuals With Euthyroidism or Subclinical Hypothyroidism With Measured Thyroid Antibodies

Study	Description of Study Sample	n	Median Age, Range[a]	Women, n, %	Subclinical Hypothyroidism, n, %[b]	Subclinical Hypothyroidism With Positive TPOAbs, n, %[c]	Thyroid Medication at Baseline/During Follow-Up, n, %[d]	Follow-Up[e]	
								Start	Median Duration (IQR)/Person-Years
United States									
Cardiovascular Health Study (22)	Community-dwelling adults with Medicare eligibility in four US communities	2984	71 (64–100)	1788 (59.9%)	458 (15.3%)	187 (40.8%)	0 (0.0%)/ 146 (4.9%)	1989–1990	13.9 (8.6–16.4)/ 36 584
Europe									
HUNT Study (16)	Adults living in Nord-Trøndelag County, Norway	26 062	54 (20–97)	17 562 (67.4%)	822 (3.2%)	429 (52.2%)	0 (0.0%)/ NA	1995–1997	12.3 (11.8–12.9)/ 305 106
Study of Health in Pomerania (24)	Adults living in Western Pomerania, Germany	3845	49 (20–81)	1945 (50.6%)	106 (2.8%)	32 (30.2%)	206 (5.4%)/ 262 (6.8%)	1997–2001	10.0 (9.3–10.7)/ 37 209
Whickham Survey (14)	Adults living in and near Newcastle upon Tyne, UK	2406	46 (18–92)	1284 (53.4%)	124 (5.2%)	41 (33.1%)	99 (4.1%)/ 73 (3.0%)	1972–1974	19.0 (15.0–20.0)/ 39 088
Australia									
Busselton Health Study (15)	Adults living in Busselton, Western Australia	1997	51 (18–90)	983 (49.2%)	89 (4.5%)	60 (67.4%)	15 (0.8%)/ 33 (1.7%)	1981	20.0 (19.5–20.0)/ 35 437
Brazil									
Brazilian Thyroid Study (35)	Adults of Japanese descent living in São Paulo, Brazil	980	56 (30–92)	518 (52.9%)	92 (9.4%)	26 (28.3%)	0 (0.0%)/ NA	1999–2000	7.3 (7.1–7.5)/ 6909
Overall		38 274	55 (18–100)	24 080 (62.9%)	1691 (4.4%)	775 (45.8%)	320 (0.8%)/ 514 (1.3%)	1972–2001	12.2 (11.2–13.1)/ 460 333

Abbreviations: IQR, interquartile range (25th to 75th percentiles); NA, data not available.

[a] Participants younger than 18 years were excluded.

[b] The Whickham Survey used a first-generation TSH assay, which gives higher values than current assays; thus, a TSH range of 6.0–21.5 mIU/L was used for subclinical hypothyroidism (14). Participants in Study of Health in Pomerania had iodine supplementation a few years before inclusion; thus, a TSH reference range (0.25–2.12 mIU/L) was used as suggested (25).

[c] Number of participants with subclinical hypothyroidism and a positive TPOAb status. The percentage relates to all participants with subclinical hypothyroidism (shown immediately to the left of this column).

[d] Data on thyroid medication use (T_4, antithyroid drugs) were not available for 2 and 1468 participants of the Whickham Survey (14) at baseline and during follow-up, respectively, and for all participants of the HUNT Study (16) and the Brazilian Thyroid Study (35) during follow-up.

[e] For all cohorts, we used the maximal follow-up data that were available, which might differ from previous reports for some cohorts.

according to sex and age, although the interaction terms were not statistically significant (*P* for interaction ≥.39 for sex and *P* for interaction >.05 for age categories, Tables 2 and 3).

Sensitivity analyses yielded comparable results (Table 4). The exclusion of thyroid medication users at baseline or during follow-up yielded similar results including after further excluding two studies without data on thyroid medication during follow-up (16, 35) (data not shown). Risks were similar in multivariate models accounting for cardiovascular risk factors, lipid-lowering and antihypertensive medications, or BMI. Limiting analyses to studies with recent thyroid antibodies assays or to participants with TSH of 10.0 mIU/L or greater yielded overall higher risks of CHD mortality and events, but estimates did not differ according to TPOAb status (Supplemental Appendix Table 2).

When analyzing data from the four cohorts that measured TPOAbs in all participants, irrespective of TSH (n = 9151) (14, 15, 24, 35), the overall prevalence of TPOAb positivity was 6.5% (Supplemental Appendix Table 3). In age- and sex-adjusted analyses, CHD mortality risk was similar in the population with positive TPOAbs compared with those with negative TPOAbs (HR 1.09, CI 0.75–1.58) as well as for CHD events (HR 1.19, CI 0.93–1.53). Stratified analyses by gender yielded similar results (both *P* for interaction ≥.40). This post hoc analysis showed similar results to the main analyses of subclinical hypothyroidism according to TPOAb status, with lower power due to the number of participants.

One study had data on thyroid antibodies and incident HF events (22). Among the 2985 older participants, 695 (27.5%) individuals in the euthyroid state and 116 (25.3%) with subclinical hypothyroidism developed HF.

Table 2. Age- and Sex-Adjusted Analyses for the Association of SH With CHD Mortality, According to Measured Thyroid Antibody Status

	CHD Mortality[a]								
	Euthyroidism		SH With Negative TPOAb Status		SH With Positive TPOAb Status		SH With Negative TPOAb vs Euthyroidism HR (95% CI)	SH With Positive TPOAb vs Euthyroidism HR (95% CI)	*P* for Interaction
	Events	Participants	Events	Participants	Events	Participants			
Total population	1301	36 583	85	916	50	775	1.26 (1.01–1.58)	1.15 (0.87–1.53)	.62
Sex									
Men	720	13 720	38	322	19	152	1.16 (0.84–1.62)	1.38 (0.80–2.37)	.59
Women	581	22 863	47	594	31	623	1.41 (1.04–1.90)	1.21 (0.84–1.73)	.53
P for interaction							.39	.70	
Age, y[b]									
18–49	50	11 704	1	173	1	162	2.41 (0.55–10.61)[c]	4.88 (1.20–19.96)[c]	.50
50–64	210	11 210	10	221	4	196	2.71 (1.12–6.53)[c]	1.83 (0.72–4.63)[c]	.55
65–79	805	9630	64	432	34	344	1.49 (1.15–1.93)	1.04 (0.74–1.47)	.10
≥80	212	1381	10	88	11	41	0.60 (0.32–1.13)[c]	1.71 (0.92–3.19)[c]	.02
P for trend							.057	.12	
TSH									
0.45–4.49 mIU/L	1301	36 583					1 (reference)	1 (reference)	
4.5–6.9 mIU/L			69	733	23	475	1.39 (1.09–1.78)	1.11 (0.71–1.74)	.39
7.0–9.9 mIU/L			11	133	13	173	1.09 (0.47–2.54)[c]	1.28 (0.75–2.18)[c]	.75
10.0–19.9 mIU/liter			5	50	14	120	1.64 (0.75–3.56)[c]	1.70 (1.01–2.86)[c]	.94
P for trend							.33	.047	

Abbreviation: SH, subclinical hypothyroidism.

[a] Twenty-one participants were excluded from the analyses of CHD mortality because of missing cause of death.

[b] These HRs were adjusted for sex and age as a continuous variable to avoid residual confounding within age strata.

[c] Strata from specific studies were excluded when there were fewer than five events or an empty comparison group.

Age- and gender-adjusted analyses stratified by thyroid antibodies showed similar HF risks among those with thyroid antibody-positive subclinical hypothyroidism (HR 0.84, CI 0.61–1.14) and those with thyroid antibody-negative subclinical hypothyroidism (HR 1.01, CI 0.79–1.28, *P* for interaction = .37). Power was insufficient to assess HF risks stratified by both thyroid antibodies and TSH levels or other subgroups.

Table 3. Age- and Sex-Adjusted Analyses for the Association of SH With CHD Events, According to Measured Thyroid Antibody Status

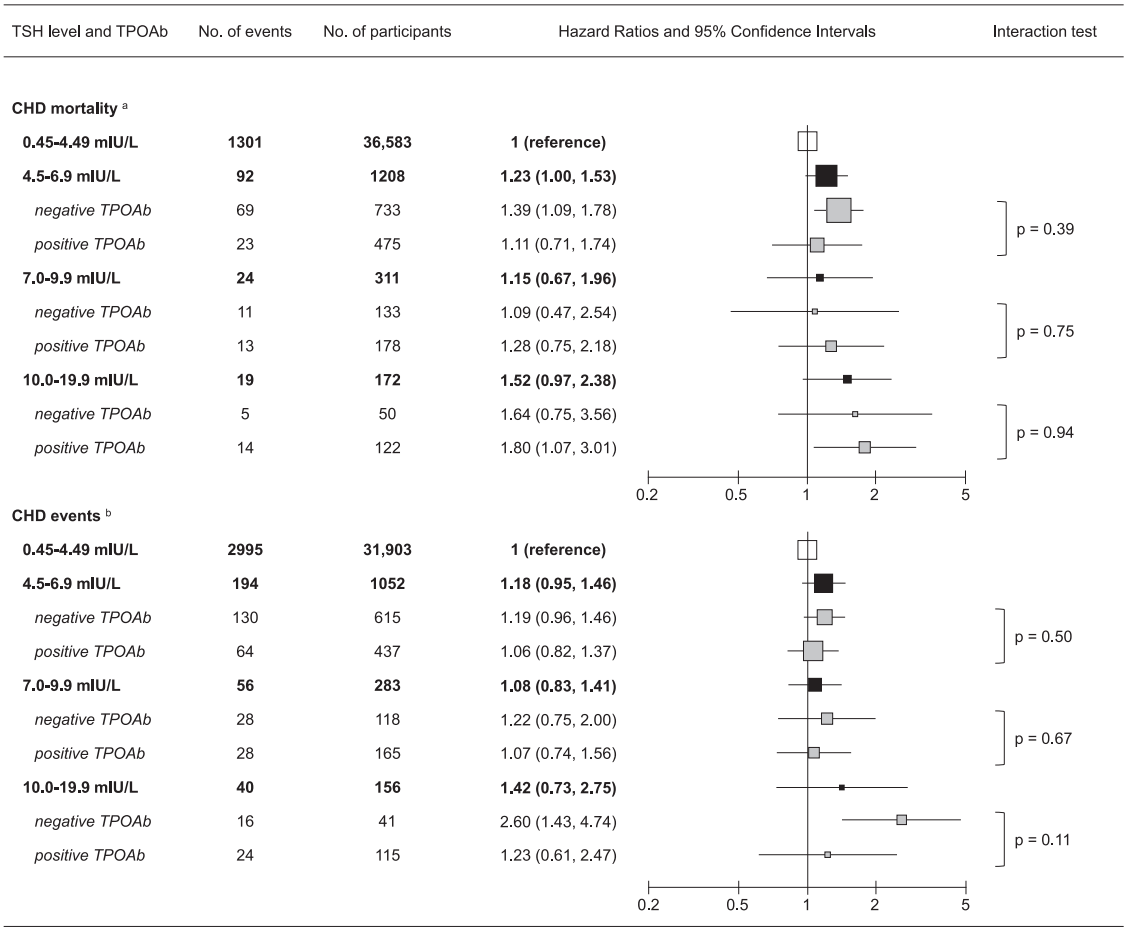
	CHD Events[a]								
	Euthyroidism		SH With Negative TPOAb Status		SH With Positive TPOAb Status		SH With Negative TPOAb vs Euthyroidism HR (95% CI)	SH With Positive TPOAb vs Euthyroidism HR (95% CI)	*P* for Interaction
	Events	Participants	Events	Participants	Events	Participants			
Total population	2995	31 903	174	774	116	717	1.26 (1.02–1.56)	1.16 (0.87–1.56)	.65
Sex									
Men	1609	11 392	79	273	36	133	1.16 (0.92–1.46)	0.99 (0.66–1.48)	.51
Women	1386	20 511	95	501	80	584	1.27 (1.02–1.59)	1.18 (0.94–1.48)	.65
P for interaction							.58	.46	
Age, y[b]									
18–49	322	11 697	6	122	7	161	1.44 (0.66–3.14)	2.13 (1.00–4.55)	.48
50–64	660	10 160	21	164	10	185	1.72 (1.10–2.69)[c]	0.98 (0.38–2.54)[c]	.29
65–79	1686	8627	123	400	84	330	1.20 (1.00–1.45)	1.11 (0.79–1.56)	.69
≥80 y	306	1380	24	88	15	41	1.04 (0.68–1.57)[c]	1.54 (0.63–3.75)[c]	.44
P for trend							.33	.65	
TSH									
0.45–4.49 mIU/L	2995	31 903					1 (reference)	1 (reference)	
4.5–6.9 mIU/L			130	615	64	437	1.19 (0.96–1.46)	1.06 (0.82–1.37)	.50
7.0–9.9 mIU/L			28	118	28	165	1.22 (0.75–2.00)	1.07 (0.74–1.56)	.67
10.0–19.9 mIU/L			16	41	24	115	2.60 (1.43–4.74)	1.23 (0.61–2.47)	.11
P for trend							.002	.57	

Abbreviation: SH, subclinical hypothyroidism.

[a] The Study of Health in Pomerania (24) and the Brazil Thyroid Study (35) were not included in CHD events analysis because follow-up data were only available for death.

[b] These HRs were adjusted for sex and age as a continuous variable to avoid residual confounding within age strata.

[c] Strata from specific studies were excluded when there were fewer than five events or an empty comparison group.



Age and gender-adjusted hazard ratios are represented by squares with size proportional to the inverse of the variance of the hazard ratio. Squares to the right of the vertical line indicate increased CHD risk compared to the reference category (identified by unfilled squares, not to scale to improve readability). Horizontal lines represent 95% confidence intervals.

[a] 21 participants were excluded from the analyses of CHD mortality because of missing cause of death.

[b] SHIP and the Brazil Thyroid Study were not included in CHD events analysis, because follow-up data were only available for death.

Figure 1. Hazard ratios of CHD mortality and events for subclinical hypothyroidism vs euthyroidism, according to TSH level and TPOAb status.

The proportional hazard assumption was consistent across studies (all $P > .10$). We found limited evidence of publication bias with visual assessment of age- and gender-adjusted funnel plots and the Egger test for CHD mortality ($P = .50$) and CHD events ($P = .060$).

Discussion

In this analysis of data from more than 38 000 individuals recruited in six prospective cohorts, risks of CHD mortality and CHD events associated with subclinical hypothyroidism did not differ according to TPOAb status. In stratified analyses, risks increased with higher TSH levels but did not differ by TPOAb status at each TSH level.

These results are consistent with most previous studies. In a recent analysis, LeGrys et al (17) found no association between the presence of TPOAbs in subclinical hypothyroidism and subsequent MI events among postmenopausal women. Similar results were also found for reports of single cohorts included in the Thyroid Studies Collaboration, such as the Whickham Survey (14), the Nord-Trøndelag Health Study (HUNT) (16), and the Busselton Health Study (15). However, in the Rotterdam Study, the presence of positive TPOAbs in subclinical hypothyroidism was associated with prevalent MI compared with euthyroid women (18), but there were not enough events for a prospective analysis of this association (16 first incident MIs over 4.6 y) (21).

Because thyroid autoimmunity has been associated with a higher risk for progression from subclinical to overt hypothyroidism (6–10), progression of atherosclerosis (18, 36), and overt hypothyroidism with increased cardiovascular risk (12), one may expect that TPOAb-positive subclinical hypothyroidism would also be associated with more CHD mortality or events. This was not confirmed in our analysis. A possible explanation is that physicians may rely on TPOAb status to decide whether to start levothyroxine treatment, as recommended by some current guidelines (3), and that such treatment may have reduced the risk of CHD. However, our sensitivity anal-

Table 4. Sensitivity Analyses for the Association of SH With CHD Mortality and CHD Events, According to Measured Thyroid Antibody Status

	Euthyroidism		SH With Negative TPOAb Status		SH With Positive TPOAb Status		SH With Negative TPOAb vs Euthyroidism HR (95% CI)	SH With Positive TPOAb vs Euthyroidism HR (95% CI)	*P* for Interaction
	Events	Participants	Events	Participants	Events	Participants			
CHD mortality									
All eligible studies									
Random-effects model	1301	36 583	85	916	50	775	1.26 (1.01–1.58)	1.15 (0.87–1.53)	.62
Fixed-effects model	1301	36 583	85	916	50	775	1.26 (1.01–1.58)	1.15 (0.87–1.53)	.62
Excluding participants									
Excluding those with missing T_4[a]	1301	36 583	84	912	49	771	1.26 (1.00–1.57)	1.13 (0.85–1.51)	.56
Excluding thyroid medication users at baseline[b]	1279	36 289	83	899	49	766	1.26 (1.01–1.58)	1.13 (0.85–1.51)	.53
Excluding thyroid medication users at baseline or during follow-up[b]	1269	36 076	78	834	44	682	1.34 (1.07–1.69)	1.28 (0.94–1.72)	.79
Excluding studies									
Excluding studies with older thyroid antibody assays[c]	711	31 775	32	562	17	547	1.56 (1.09–2.23)	1.21 (0.75–1.94)	.41
Excluding study with recent iodine supplementation (24)	1247	32 844	84	842	50	743	1.26 (1.01–1.57)	1.15 (0.86–1.53)	.62
Excluding studies with shifted TSH reference range (14, 24)	1024	30 562	74	759	44	702	1.30 (1.02–1.65)	1.13 (0.84–1.53)	.47
Further adjustments in MV models[d]									
Adjusted for age, sex, systolic blood pressure, smoking status, total cholesterol, and diabetes at baseline (MV model 1)	1290	36 441	84	914	50	772	1.27 (1.01–1.59)	1.16 (0.88–1.55)	.62
MV model 1 + lipid-lowering and antihypertensive medications	1287	36 373	84	912	50	772	1.26 (1.01–1.58)	1.18 (0.89–1.57)	.72
MV model 1 + BMI	1276	36 234	82	908	48	776	1.25 (1.00–1.57)	1.13 (0.84–1.50)	.59
CHD events									
All eligible studies									
Random-effects model	2995	31 903	174	774	116	717	1.26 (1.02–1.56)	1.16 (0.87–1.56)	.65
Fixed-effects model	2995	31 903	174	774	116	717	1.20 (1.03–1.41)	1.08 (0.90–1.31)	.39
Excluding participants									
Excluding those with missing T_4[a]	2995	31 903	172	770	115	713	1.26 (1.01–1.56)	1.17 (0.86–1.59)	.70
Excluding thyroid medication users at baseline[b]	2967	31 805	172	768	115	711	1.24 (1.02–1.51)	1.15 (0.8–1.54)	.67
Excluding thyroid medication users at baseline or during follow-up[b]	2934	31 695	155	715	93	638	1.25 (1.06–1.47)	1.12 (0.88–1.41)	.46
Excluding studies									
Excluding studies with older thyroid antibody assays[c]	1599	27 138	54	422	40	489	1.49 (1.13–1.95)	1.28 (0.74–2.22)	.63
Excluding study with recent iodine supplementation (24)	NA	NA	NA	NA	NA	NA	NA	NA	
Excluding studies with shifted TSH reference range (14, 24)	2557	29 664	157	693	106	677	1.29 (0.97–1.71)	1.12 (0.80–1.59)	.53
Further adjustments in multivariate models[d]									
Adjusted for age, sex, systolic blood pressure, smoking status, total cholesterol, and diabetes at baseline (MV model 1)	2978	31 784	173	772	116	715	1.28 (1.02–1.59)	1.17 (0.86–1.59)	.65
MV model 1 + lipid-lowering and antihypertensive medications	2974	31 716	173	770	116	714	1.29 (1.03–1.61)	1.22 (0.88–1.70)	.78
MV model 1 + BMI	2940	31 587	169	766	114	709	1.23 (1.01–1.50)	1.17 (0.87–1.58)	.78

Abbreviations: MV, multivariate; NA, not applicable; SH, subclinical hypothyroidism.

[a] Eight participants were excluded in this analysis: six in the Cardiovascular Health Study, one in the Whickham Survey, and one in the Busselton Health Study.

[b] The numbers of thyroid medication users (T_4, antithyroid drugs) at baseline and during follow-up are reported in Table 1.

[c] Studies with older thyroid autoantibodies assays were excluded: antimicrosomal antibodies in the Cardiovascular Health Study (22) and thyroid cytoplasmic antibodies in the Whickham Survey (14).

[d] Some participants were excluded from the MV models because of lack of data on covariates.

ysis yielded similar results after excluding participants who started thyroid medication during follow-up. Moreover, some of the etiologies of TPOAb-negative subclinical hypothyroidism may also increase CHD risk. For example, adiposity is probably one of the causes of elevated TSH levels (37), and adiposity is also associated with increased CHD risk (38). However, adjusting for BMI (our best measure of adiposity) did not change the present results. To summarize, the presence of TPOAb may be a good marker of progression of subclinical to overt hypothyroidism, but a poor marker for stratification of who will develop cardiovascular complications (3). Our analyses show that any risk of CHD is mediated through thyroid dysfunction (5), without an independent contribution from autoimmune dysfunction. This adds to the current knowledge about the pathophysiology of thyroid-related CHD and has clinical implications because thyroid dysfunction is a treatable risk factor and thyroid autoimmunity is not.

Our study is the largest to investigate the association between TPOAb status and cardiovascular risk in participants with subclinical hypothyroidism. The analysis of individual participant data from several studies allowed us to analyze subgroup data that have less potential bias than study-level meta-analyses. Study strengths are the inclusion of time-to-event analyses and the use of standardized definitions of predictors, outcomes, and adjustment for confounding factors (29).

The study had the following limitations. Participants were mainly Caucasians, except for one cohort including Brazilians of Japanese descent (35), so our results may not apply to other populations. Second, thyroid function tests were performed only at baseline, which is a limitation of most published cohort studies. The number of participants with subclinical hypothyroidism at baseline that normalized to euthyroid state over time or those who progressed to overt hypothyroidism is unknown, although previous studies showed a low proportion of progression over 20 years of follow-up (14). Moreover, recent studies found similar results for risk of CHD using single or repeated TSH measurements among the elderly within the Cardiovascular Health Study (28). In a recent study of the oldest old, there were no associations between baseline levels and a 13-year change in TSH, free T_4 levels, and TPOAb positivity and mortality (39). Third, older thyroid antibodies assays were used in two included cohorts [antimicrosomal antibodies (22) and thyroid cytoplasmic antibodies (14)], but sensitivity analyses excluding cohorts with older assays yielded similar results. Because thyroglobulin antibodies (TgAbs) were not available in the three largest cohorts, there was insufficient power to examine the risks associated with thyroglobulin antibodies. However, the lack of TgAbs in our analyses should not be a major limitation because most people (70%) who had positive TgAbs in National Health and Nutrition Examination Survey III also had positive TPOAbs (2). Moreover, both in the National Health and Nutrition Examination Survey III [cross-sectional (2)] and the Busselton Health Study [longitudinal analysis (40)], a positive TgAb alone in the absence of positive TPOAb was not a predictor of thyroid disease. Fourth, during follow-up of individuals with subclinical hypothyroidism, 90 of the 294 participants with positive thyroid antibodies (30.6%) and 67 of the 378 participants with negative thyroid antibodies (17.7%) were treated with T_4. However, sensitivity analyses excluding thyroid medication users yielded similar results.

Current guidelines for the management of subclinical hypothyroidism are conflicting about measuring TPOAbs to target treatment in patients with subclinical hypothyroidism (1, 3). Although the presence of TPOAbs in subclinical hypothyroidism predicts the evolution to overt hypothyroidism, we found that it did not predict CHD outcomes associated with subclinical hypothyroidism, suggesting that biomarkers of thyroid autoimmunity do not add independent prognostic information on CHD outcomes. Thyroid antibodies may be useful for investigating the etiology of subclinical hypothyroidism and to predict the potential evolution to overt hypothyroidism. Because of the absence of prediction of TPOAb status on CHD risks in subclinical hypothyroidism, other biomarkers should be examined to identify patients at increased cardiovascular risk. Randomized clinical trials are needed to clarify whether the presence of thyroid antibodies to target treatment in patients predicts a larger benefit of levothyroxine treatment of subclinical hypothyroidism on clinical outcomes (4, 41).

Acknowledgments

Address all correspondence and requests for reprints to: Nicolas Rodondi, MD, MAS, Department of General Internal Medicine, Bern University Hospital, and University of Bern, 3000 Bern, Switzerland. E-mail: nicolas.rodondi@insel.ch.

This work was supported by Grants SNSF 320030-138267 and 320030-150025 from the Swiss National Science Foundation and partially supported by a grant from the Swiss Heart Foundation (all to N.R.). The research by T.-H.C. is supported by Grant PBLAP3-145870 from the Swiss National Science Foundation. The Cardiovascular Health Study and the research reported in this article were supported by Contracts N01-HC-80007 and N01-HC-85079 through Grants N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, and N01-HC-45133 and Grant U01 HL080295 from the National Heart, Lung, and Blood Institute, with additional contribution from the National Institute of Neurological Disorders

and Stroke. Additional support was provided through Grants R01 AG-15928, R01 AG-20098, AG-027058, and AG-032317 from the National Institute on Aging, Grant R01 HL-075366 from the National Heart, Lung, and Blood Institute, and the University of Pittsburgh Claude D. Pepper Older Americans Independence Center Grant P30-AG-024827. The thyroid measurements in the Cardiovascular Health Study were supported by an American Heart Association Grant-in-Aid (to Dr Linda Fried). Analyses were further supported by Grant DFG Vo 955/12-1 from the German Research Foundation as well by the German Centre for Cardiovascular Research and the German Ministry of Education and Research. The Brazilian Thyroid Study was supported by an unrestricted grant from the Sao Paulo State Research Foundation (Fundacão de Amparo à Pesquisa do Estado de Sao Paulo, FAPESP, Grant 6/59737-9 to R.M.B.M.). A.B.N. is supported by Grant AG-023629 from the National Institute on Aging.

Participating studies of the Thyroid Studies Collaboration include the following: United States: Cardiovascular Health Study (CHS); Norway: The HUNT Study (Nord-Trøndelag Health Study); Germany: Study of Health in Pomerania (SHIP); United Kingdom: Whickham Survey; Australia: Busselton Health Study; and Brazil: Brazilian Thyroid Study.

A full list of principal CHS investigators and institutions can be found at https://chs-nhlbi.org/pi. The HUNT Study (Nord-Trøndelag Health Study Study) is a collaborative effort of HUNT Research Center, Faculty of Medicine, Norwegian University of Science and Technology; Nord-Trøndelag County Council; Central Norway Health Authority; and the Norwegian Institute of Public Health. Data were provided by the HUNT Research Center, Statistics Norway, and the Department for Research and Development, Nord-Trøndelag Hospital Trust. The thyroid function testing in the HUNT Study was financially supported by Wallac Oy (Turku, Finland). The Study of Health in Pomerania (SHIP) is part of the Community Medicine Research net of the University of Greifswald, Germany, which is funded by the Federal Ministry of Education and Research and the Ministry of Cultural Affairs as well as the Social Ministry of the Federal State of Mecklenburg-West Pomerania. Analyses were further supported by a grant of the German Research Foundation as well by the German Centre for Cardiovascular Research and by the German Ministry of Education and Research. This work is also part of the research project Greifswald Approach to Individualized Medicine (GANI_MED).

None of the sponsors had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

Each of the original cohort studies has been approved by its respective institutional review board.

Dr Vittinghoff (Professor of Biostatistics, Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California) reviewed the statistical analyses of the manuscript and is included in the authors of the manuscript.

T.-H.C. and N.R. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

N.R., D.C.B., J.G., A.R.C. were responsible for the study concept and design.

Acquisition of data were conducted by J.G., A.R.C., B.O.Å., J.A.S., H.V., and J.P.W.

Analysis and interpretation of data were conducted by T.-H.C., D.C.B., A.R.C., S.W., E.V., J.G., B.O.Å., A.B., W.P.d.E., R.M.B.M., M.P.J.V., M.D., H.W., A.B.N., J.A.S., S.R., H.V., J.P.W., D.A., and N.R.

Drafting of the manuscript was performed by T.-H.C. and N.R.

Critical revision of the manuscript for important intellectual content was conducted by T.-H.C., D.C.B., A.R.C., S.W., E.V., J.G., B.O.Å., A.B., W.P.d.E., R.M.B.M., M.P.J.V., M.D., H.W., A.B.N., J.A.S., S.R., H.V., J.P.W., D.A., and N.R.

Statistical analyses were performed by T.-H.C., N.R., and E.V.

Funding was obtained by N.R., J.G., B.O.Å, J.A.S., H.V., A.B.N., and J.P.W.

Administrative, technical, or material support was provided by N.R. and J.G.

Study supervision was provided N.R. and D.C.B.

Disclosure Summary: The authors declare no financial relationship with any organization that might have an interest in the submitted work in the previous 3 years; their spouses, partners, or children have no financial relationship that may be relevant to the submitted work; there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. **Surks MI, Ortiz E, Daniels GH, et al.** Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA*. 2004;291:228–238.
2. **Hollowell JG, Staehling NW, Flanders WD, et al.** Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*. 2002;87:489–499.
3. **Garber JR, Cobin RH, Gharib H, et al.** Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocr Pract*. 2012;18:988–1028.
4. **Villar HC, Saconato H, Valente O, Atallah AN.** Thyroid hormone replacement for subclinical hypothyroidism. *Cochrane Database Syst Rev*. 2007:CD003419.
5. **Rodondi N, den Elzen WP, Bauer DC, et al.** Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA*. 2010;304:1365–1374.
6. **Vanderpump MP, Tunbridge WM, French JM, et al.** The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin Endocrinol (Oxf)*. 1995;43:55–68.
7. **Diez JJ, Iglesias P.** Spontaneous subclinical hypothyroidism in patients older than 55 years: an analysis of natural course and risk factors for the development of overt thyroid failure. *J Clin Endocrinol Metab*. 2004;89:4890–4897.
8. **Li Y, Teng D, Shan Z, et al.** Antithyroperoxidase and antithyroglobulin antibodies in a five-year follow-up survey of populations with different iodine intakes. *J Clin Endocrinol Metab*. 2008;93:1751–1757.

9. **Somwaru LL, Rariy CM, Arnold AM, Cappola AR.** The natural history of subclinical hypothyroidism in the elderly: the Cardiovascular Health Study. *J Clin Endocrinol Metab*. 2012;97:1962–1969.
10. **Huber G, Staub JJ, Meier C, Mitrache C, Guglielmetti M, Huber P, Braverman LE.** Prospective study of the spontaneous course of subclinical hypothyroidism: prognostic value of thyrotropin, thyroid reserve, and thyroid antibodies. *J Clin Endocrinol Metab*. 2002;87:3221–3226.
11. **McDermott MT, Haugen BR, Lezotte DC, Seggelke S, Ridgway EC.** Management practices among primary care physicians and thyroid specialists in the care of hypothyroid patients. *Thyroid*. 2001;11:757–764.
12. **Biondi B, Klein I.** Hypothyroidism as a risk factor for cardiovascular disease. *Endocrine*. 2004;24:1–13.
13. **Taddei S, Caraccio N, Virdis A, et al.** Low-grade systemic inflammation causes endothelial dysfunction in patients with Hashimoto's thyroiditis. *J Clin Endocrinol Metab*. 2006;91:5076–5082.
14. **Vanderpump MP, Tunbridge WM, French JM, et al.** The development of ischemic heart disease in relation to autoimmune thyroid disease in a 20-year follow-up study of an English community. *Thyroid*. 1996;6:155–160.
15. **Walsh JP, Bremner AP, Bulsara MK, et al.** Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. *Arch Intern Med*. 2005;165:2467–2472.
16. **Asvold BO, Bjoro T, Platou C, Vatten LJ.** Thyroid function and the risk of coronary heart disease: 12-year follow-up of the HUNT Study in Norway. *Clin Endocrinol (Oxf)*. 2012;77(6):911–9117.
17. **LeGrys VA, Funk MJ, Lorenz CE, et al.** Subclinical hypothyroidism and risk for incident myocardial infarction among postmenopausal women. *J Clin Endocrinol Metab*. 2013;98:2308–2317.
18. **Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC.** Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. *Ann Intern Med*. 2000;132:270–278.
19. **Collet TH, Gussekloo J, Bauer DC, et al.** Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. *Arch Intern Med*. 2012;172:799–809.
20. **Gencer B, Collet TH, Virgini V, et al.** Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. *Circulation*. 2012;126:1040–1049.
21. **Ochs N, Auer R, Bauer DC, et al.** Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. *Ann Intern Med*. 2008;148:832–845.
22. **Cappola AR, Fried LP, Arnold AM, et al.** Thyroid status, cardiovascular risk, and mortality in older adults. *JAMA*. 2006;295:1033–1041.
23. **Nicoloff JT, Spencer CA.** Clinical review 12: the use and misuse of the sensitive thyrotropin assays. *J Clin Endocrinol Metab*. 1990;71:553–558.
24. **Ittermann T, Haring R, Sauer S, Wallaschofski H, Dorr M, Nauck M, Volzke H.** Decreased serum TSH levels are not associated with mortality in the adult northeast German population. *Eur J Endocrinol*. 2010;162:579–585.
25. **Volzke H, Alte D, Kohlmann T, et al.** Reference intervals of serum thyroid function tests in a previously iodine-deficient area. *Thyroid*. 2005;15:279–285.
26. **Mariotti S, Caturegli P, Piccolo P, Barbesino G, Pinchera A.** Antithyroid peroxidase autoantibodies in thyroid diseases. *J Clin Endocrinol Metab*. 1990;71:661–669.
27. **Grundy SM.** Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
28. **Hyland KA, Arnold AM, Lee JS, Cappola AR.** Persistent subclinical hypothyroidism and cardiovascular risk in the elderly: the cardiovascular health study. *J Clin Endocrinol Metab*. 2013;98:533–540.
29. **Simmonds MC, Higgins JP, Stewart LA, Tierney JF, Clarke MJ, Thompson SG.** Meta-analysis of individual patient data from randomized trials: a review of methods used in practice. *Clin Trials*. 2005;2:209–217.
30. **Riley RD, Lambert PC, Abo-Zaid G.** Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ*. 2010;340:c221.
31. **Higgins JP, Thompson SG, Deeks JJ, Altman DG.** Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
32. **Heinze G, Schemper M.** A solution to the problem of monotone likelihood in Cox regression. *Biometrics*. 2001;57:114–119.
33. **Schoenfeld D.** Chi-squared goodness-of-fit tests for the proportional hazards regression model. *Biometrika*. 1980;67:145–153.
34. **Egger M, Davey Smith G, Schneider M, Minder C.** Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634.
35. **Sgarbi JA, Matsumura LK, Kasamatsu TS, Ferreira SR, Maciel RM.** Subclinical thyroid dysfunctions are independent risk factors for mortality in a 7.5-year follow-up: the Japanese-Brazilian thyroid study. *Eur J Endocrinol*. 2010;162:569–577.
36. **Ciccone MM, De Pergola G, Porcelli MT, et al.** Increased carotid IMT in overweight and obese women affected by Hashimoto's thyroiditis: an adiposity and autoimmune linkage? *BMC Cardiovasc Disord*. 2010;10:22.
37. **Fox CS, Pencina MJ, D'Agostino RB, et al.** Relations of thyroid function to body weight: cross-sectional and longitudinal observations in a community-based sample. *Arch Intern Med*. 2008;168:587–592.
38. **Whitlock G, Lewington S, Sherliker P, et al.** Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet*. 2009;373:1083–1096.
39. **Waring AC, Arnold AM, Newman AB, Buzkova P, Hirsch C, Cappola AR.** Longitudinal changes in thyroid function in the oldest old and survival: the Cardiovascular Health Study All-Stars Study. *J Clin Endocrinol Metab*. 2012;97:3944–3950.
40. **Walsh JP, Bremner AP, Feddema P, Leedman PJ, Brown SJ, O'Leary P.** Thyrotropin and thyroid antibodies as predictors of hypothyroidism: a 13-year, longitudinal study of a community-based cohort using current immunoassay techniques. *J Clin Endocrinol Metab*. 2010;95:1095–1104.
41. **Rodondi N, Bauer DC.** Subclinical hypothyroidism and cardiovascular risk: how to end the controversy. *J Clin Endocrinol Metab*. 2013;98:2267–2269.