Review

Subclinical Hypothyroidism and the Risk of Stroke Events and Fatal Stroke: An Individual Participant Data Analysis

Layal Chaker, Christine Baumgartner, Wendy P. J. den Elzen, M. Arfan Ikram, Manuel R. Blum, Tinh-Hai Collet, Stephan J. L. Bakker, Abbas Dehghan, Christiane Drechsler, Robert N. Luben, Albert Hofman, Marileen L. P. Portegies, Marco Medici, Giorgio Iervasi, David J. Stott, Ian Ford, Alexandra Bremner, Christoph Wanner, Luigi Ferrucci, Anne B. Newman, Robin P. Dullaart, José A. Sgarbi, Graziano Ceresini, Rui M. B. Maciel, Rudi G. Westendorp, J. Wouter Jukema, Misa Imaizumi, Jayne A. Franklyn, Douglas C. Bauer, John P. Walsh, Salman Razvi, Kay-Tee Khaw, Anne R. Cappola, Henry Völzke, Oscar H. Franco, Jacobijn Gussekloo, Nicolas Rodondi, and Robin P. Peeters,* for the Thyroid Studies Collaboration

Objective: The objective was to determine the risk of stroke associated with subclinical hypothyroidism.

Data Sources and Study Selection: Published prospective cohort studies were identified through a systematic search through November 2013 without restrictions in several databases. Unpublished studies were identified through the Thyroid Studies Collaboration. We collected individual participant data on thyroid function and stroke outcome. Euthyroidism was defined as TSH levels of 0.45–4.49 mIU/L, and subclinical hypothyroidism was defined as TSH levels of 4.5–19.9 mIU/L with normal T_4 levels.

Data Extraction and Synthesis: We collected individual participant data on 47 573 adults (3451 subclinical hypothyroidism) from 17 cohorts and followed up from 1972–2014 (489 192 person-years). Age- and sex-adjusted pooled hazard ratios (HRs) for participants with subclinical hypothyroidism compared to euthyroidism were 1.05 (95% confidence interval [CI], 0.91–1.21) for stroke events (combined fatal and nonfatal stroke) and 1.07 (95% CI, 0.80–1.42) for fatal stroke. Stratified by age, the HR for stroke events was 3.32 (95% CI, 1.25–8.80) for individuals aged 18–49 years. There was an increased risk of fatal stroke in the age groups 18–49 and 50–64 years, with a HR of 4.22 (95% CI, 1.08–16.55) and 2.86 (95% CI, 1.31–6.26), respectively (p trend 0.04). We found no increased risk for those 65–79 years old (HR, 1.00; 95% CI, 0.86–1.18) or ≥80 years old (HR, 1.31; 95% CI, 0.79–2.18). There was a pattern of increased risk of fatal stroke with higher TSH concentrations.

Conclusions: Although no overall effect of subclinical hypothyroidism on stroke could be demonstrated, an increased risk in subjects younger than 65 years and those with higher TSH concentrations was observed. (***J Clin Endocrinol Metab*** **100: 2181–2191, 2015)**

Subclinical hypothyroidism is defined as an elevated TSH level above the upper limit of the reference range with a free T_4 (FT4) value that is normal (1–3). It has a prevalence varying between 4% and 14% in adults (4–6), with a higher prevalence in iodine-sufficient populations (7) and older individuals (5). Subclinical hypothyroidism has been associated with hypercholesterolemia (6, 8, 9), atherosclerosis (10), and an increased carotid intima-media thickness (11). Furthermore, the association between subclinical hypothyroidism and the risk of clinical

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received February 17, 2015. Accepted April 7, 2015.
First Published Online April 9, 2015

* Author Affiliations are shown at the bottom of the next page.
Abbreviations: CI, confidence interval; CVD, cardiovascular disease; FT4, free T_4; HR, hazard ratio; IPD, individual participant data.

cardiovascular outcomes such as coronary heart disease (12) and heart failure (13) has been established in specific subgroups with higher TSH levels (12). Also, higher risks of cardiovascular disease (CVD) in subclinically hypothyroid individuals have been found in younger populations, but not in the oldest old (14, 15).

Although CVD and stroke share risk factors, published data on the association between subclinical hypothyroidism and stroke are insufficient and conflicting (16). Even the largest prospective cohort studies have limited power, with most studies suffering from a lack of generalizability and inability to conduct subgroup analyses on specific age groups or different TSH levels (17–19). A recent systematic review and meta-analysis of published data showed no association between subclinical hypothyroidism and the risk of stroke (16). However, meta-analysis of aggregated published data does not always allow for examination of specific subgroups that may have differential risk. Hence, we aimed to evaluate the association between subclinical hypothyroidism and stroke by conducting an individual participant data (IPD) analysis, with prespecified stratified analyses to examine the effects of age, sex, and degree of TSH elevation on this association.

Materials and Methods

Data sources and study selection

We conducted a systematic review and meta-analysis, contacted experts in the field, and reviewed reference lists to identify eligible studies (16). The systematic literature search was conducted in Medline (OvidSP), EMBASE, Web-of-Science, PubMed publisher, Cochrane, and Google Scholar from inception to November 18, 2013 (Supplemental Data). We included publications from longitudinal studies that measured at least TSH and FT4 at baseline in adults and assessed stroke events and/or fatal stroke prospectively. Further details of the systematic literature search and meta-analysis have been previously described in detail elsewhere (16). We identified six studies (17–22) that met the inclusion criteria. We identified additional studies with unpublished data within the Thyroid Studies Collaboration, a consortium of cohort studies investigating the association between thyroid dysfunction and clinical outcomes. Through contact with experts in the field, we were able to identify one more unpublished study (23). Investigators from eligible studies were invited to join the IPD analysis, of which one declined to participate (22). This study included 549 euthyroid subjects with 23 stroke events and 31 subclinical hypothyroid subjects with one stroke event.

Data extraction

We requested individual participant characteristics related to prior cardiovascular risk factors and disease, including total cholesterol, systolic blood pressure (both as continuous variables), and history of diabetes, smoking, and previous cerebrovascular disease. We also collected available information on medication use (thyroid hormone replacement, antithyroid, lipid-lowering, and antihypertensive therapy), demographic information (age, sex, and ethnicity), anthropometric measurements (height and weight), and the outcome. Primary outcome measures were stroke events (fatal and nonfatal) and fatal stroke. 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 of vascular origin, including ischemic or hemorrhagic strokes. Some studies (24, 25) used variations of this definition (Supplemental Table 1).

Thyroid function testing

We used a common definition of subclinical hypothyroidism and euthyroidism to increase comparability between the different studies and in concordance with previous analyses (12, 13, 26), expert reviews (1, 3), and several large cohorts (17, 25, 27). We defined subclinical hypothyroidism as a serum TSH level of 4.5 mIU/L or greater to less than 20.0 mIU/L, with a normal FT4 concentration. Euthyroidism was defined as a TSH level between 0.45 and 4.49 mIU/L. Most studies used a third-generation TSH RIA, but the Whickham survey used a first-generation assay that reports higher measured TSH values than current assays (28), for which we adjusted the range to 6.0–21.4 mIU/L to define sub-

Department of Internal Medicine (L.C., M.M., R.P.P.), and Rotterdam Thyroid Center, Erasmus Medical Center, 3000 CA Rotterdam, The Netherlands; Department of Epidemiology (L.C., M.A.I., A.D., A.H., M.L.P.P., O.H.F.), Erasmus University Medical Center, 3000 CA Rotterdam, The Netherlands; Department of General Internal Medicine (C.B., M.R.B., N.R.), Inselspital, Bern University Hospital, 3010 Bern, Switzerland; Departments of Epidemiology, Public Health, and Primary Care (W.P.J.d.E., J.G.), Leiden University Medical Center, 2333 ZA Leiden, The Netherlands; Department of Radiology (M.A.I.), Erasmus University Medical Center, 3000 CA Rotterdam, The Netherlands; Department of Neurology (M.A.I., M.L.P.P.), Erasmus University Medical Center, 3000 CA Rotterdam, The Netherlands; Service of Endocrinology, Diabetes, and Metabolism (T.-H.C.), University Hospital of Lausanne, 1011 Lausanne, Switzerland; Department of Internal Medicine (S.J.L.B., R.P.D.), University of Groningen, University Medical Center Groningen, 9700 RB Groningen, The Netherlands; Department of Medicine (C.D., C.W.), Division of Nephrology, University Hospital of Würzburg, Germany Comprehensive Heart Failure Centre, D-97080 Würzburg, Germany; Department of Public Health and Primary Care (R.N.L., K.-T.K.), University of Cambridge, Cambridge CB2 1TN, United Kingdom; National Council Research Institute of Clinical Physiology (G.I.), Pisa 56124, Italy; Institute of Cardiovascular and Medical Sciences, Faculty of Medicine (D.J.S.), and Robertson Centre for Biostatistics (I.F.), University of Glasgow, Glasgow G12 8QQ, United Kingdom; School of Population Health (A.B.), University of Western Australia, Crawley, Perth 6009, Western Australia, Australia; National Institute on Aging (L.F.), Baltimore, Maryland 20892; Department of Epidemiology (A.B.N.), University of Pittsburgh, Pittsburgh, Pennsylvania 15260; Division of Endocrinology (J.A.S.), Faculdade de Medicina de Marília, Marília, Sao Paulo 17519, Brazil; Division of Endocrinology (J.A.S., R.M.B.M.), Department of Medicine, Federal University of Sao Paulo, Sao Paulo 04021-001, Brazil; Department of Clinical and Experimental Medicine (G.C.), University of Parma, 43125 Parma, Italy; Department of Public Health (R.G.W.), Faculty of Health and Medical Sciences, University of Copenhagen, 1165 Copenhagen, Denmark; Department of Cardiology (J.W.J.), Leiden University Medical Centre, 2333 ZA Leiden, The Netherlands; Interuniversity Cardiology Institute of the Netherlands (J.W.J.), 3511 EP Utrecht, The Netherlands; Department of Clinical Studies (M.I.), Radiation Effects Research Foundation, Nagasaki 850-0013, Japan; School of Clinical and Experimental Medicine (J.A.F.), College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT, United Kingdom; Departments of Medicine, Epidemiology, and Biostatistics and Medicine (D.C.B.), University of California, San Francisco, California 94143; Department of Endocrinology and Diabetes (J.P.W.), Sir Charles Gairdner Hospital, Nedlands, Western Australia 6009, Australia; Schools of Medicine and Pharmacology (J.P.W.), University of Western Australia, Crawley, Perth 6009, Western Australia, Australia; Department of Endocrinology (S.R.), Gateshead Health Foundation NHS Trust, Gateshead NE9 6SX, United Kingdom; Division of Endocrinology, Diabetes, and Metabolism (A.R.C.), Department of Medicine, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104; and Institute for Community Medicine (H.V.), Clinical-Epidemiological Research/SHIP, University of Medicine, 17489 Greifswald, Germany

clinical hypothyroidism, as previously described (12, 29). In addition, the Whickham survey was the only study to perform total T_4 assays (29); the remainder performed FT4 assays.

For FT4 values, we used site- and method-dependent cutoffs because these measurements are more assay dependent. We excluded participants with TSH levels below 0.45 mIU/L or above 19.9 mIU/L and those with abnormal FT4 values (n = 3967). When FT4 values were missing (n = 10 541), we considered participants with a TSH level between 4.5 and 20 mIU/L as having subclinical hypothyroidism, due to a low likelihood of overt hypothyroidism with this degree of TSH elevation (30).

Statistical analysis

We performed a Cox proportional hazard model in each cohort separately to assess the association between subclinical hypothyroidism and stroke events and fatal stroke (IBM SPSS Statistics for Windows, version 21.0; IBM Corp). The Cox proportional hazard assumption was met by each cohort, as assessed by Schoenfeld residual plots. We used a random-effects model according to DerSimonian and Laird (31) to pool estimates of the outcomes. Pooled estimates were summarized in forest plots using the metafor package for R (version 3.0.2, R-project, 2013; Institute for Statistics and Mathematics, R Core Team). Heterogeneity across studies was measured using the I^2 statistic and tested using the Q-statistic (32).

We adjusted for age and sex in the primary analysis. We also conducted a multivariable analysis additionally adjusting for systolic blood pressure, smoking, total cholesterol, and diabetes. These covariates were available in all cohorts except for the Birmingham cohort (21). We conducted multiple imputation in cohorts when there was ≥5% of missing data for the smoking, total cholesterol, systolic blood pressure, and prevalent diabetes covariates. We considered the age- and sex-adjusted analysis to be the primary analysis because: 1) covariates used in the multivariable analyses could also be considered as mediators; and 2) it includes all studies, in contrast to the multivariable analysis that does not include the Birmingham cohort.

To identify populations at risk and possible sources of heterogeneity, we conducted predefined subgroup and sensitivity analyses. We performed stratified analyses by age, sex, and degree of TSH elevation. Based on expert reviews (1, 3) and following our previous approach (12, 13), we stratified subclinical hypothyroidism into the following TSH categories: 4.5–6.9, 7.0–9.9, and 10.0–19.9 mIU/L. If a study did not have an event in the (stratified) study-specific analysis, we used Firth's penalized maximum likelihood bias reduction method for the Cox model (33, 34) to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

We conducted the following sensitivity analyses: 1) excluding three studies (20, 23, 35) that did not have stroke events (nonfatal and fatal) in the subclinical hypothyroidism group; 2) excluding participants who had thyroid function-altering medication at baseline and during follow-up; 3) excluding studies that included transient ischemic attack as a stroke event; 4) excluding participants with a history of stroke; 5) excluding participants with missing FT4 levels; 6) using only unimputed data; 7) cohorts with potential comorbidities; and 8) including the published risk estimates of the study that declined to participate in the meta-analysis (22). We assessed age- and sex-adjusted funnel plots and conducted Egger tests (36) to evaluate potential publication bias.

Results

We found 18 prospective cohort studies that met the criteria. From these we included 17 from the United States (17, 19, 35), Europe (15, 20, 21, 23, 24, 27, 29, 37–40), Australia (25), Brazil (41), and Japan (18) that prospectively assessed stroke outcomes and agreed to share individual participant data (Table 1 and Supplemental Figure 1). One study (42) was excluded from our analyses because no outcome events occurred. The included studies provided information on a total of 47 573 participants with a follow-up from 1972 to 2014, a median follow-up ranging between 1.5 and 20 years and a total follow-up of 489 192 person-years. All studies, except one (43, 44), included both female (50.8%) and male participants. The prevalence of subclinical hypothyroidism ranged from 0.4 to 16.3%, with an overall average of 7.3% (n = 3451) of which 62% were female. All cohorts reported fatal stroke, and 12 studies also reported stroke events, including fatal and nonfatal stroke, contributing to the stroke events analysis among 37 842 participants. During follow-up, 2547 stroke events occurred, and 1014 participants had fatal strokes.

All studies provided information on the proportion of participants taking thyroid medication at baseline, which varied from 0 to 8.7%. All but five studies also provided follow-up information on thyroid function-altering medication use, with a range between 0 and 12.6%. One study (24) used questionnaires for the assessment of stroke events. Formal adjudication, defined as having clear criteria for the outcomes that were reviewed by experts for each potential case, was used for stroke events in six studies (10, 15, 17, 19, 22, 40) and for fatal stroke in two additional studies (35, 39). Three studies (18, 35, 39) required multiple imputation due to more than 5% missing data for covariates.

The age- and sex-adjusted pooled HR for participants with subclinical hypothyroidism compared to euthyroidism was 1.05 (95% CI, 0.91–1.21) for stroke events and 1.07 (95% CI, 0.80–1.42) for fatal stroke (Figure 1). We found no heterogeneity for the stroke events analysis (I^2 = 0%) and little heterogeneity for fatal stroke (I^2 = 25%).

Subsequent subgroup analyses showed an increased risk of stroke events (HR, 3.32; 95% CI, 1.25–8.80) and fatal stroke (HR, 4.22; 95% CI, 1.08–16.55) in the 18- to 49-year age group with subclinical hypothyroidism compared to euthyroidism, but the number of events was small (Table 2 and Figure 2). For the 50- to 64-year age group, we found an increased risk of fatal stroke with a HR of 2.86 (95% CI, 1.31–6.26; p for trend across age groups = 0.04). When participants were pooled into two categories, younger and older than 65 years, in a post hoc analysis, we

Table 1. Baseline Characteristics of Individuals in the Included Studies (n = 47 573)

Study, Start Year (Ref.)	Description of Study Sample	n	Median Age (Range), y[a]	Women, n (%)	Subclinical Hypothyroidism, n (%)	Thyroid Medication at Baseline, n (%)[b]	Thyroid Medication Follow-Up, n (%)[c]	Median Duration (IQR), y
4D Study, 1998 (20)	Trial of atorvastatin in type 2 diabetes and hemodialysis patients, Germany	883	66 (30–83)	400 (45.3)	10 (1.1)	44 (5.0)	62 (7.0)	1.5 (0.2–3.6)
Brazilian Thyroid Study, 1999 (41)	Adults of Japanese descent living in São Paulo, Brazil	991	57 (30–92)	523 (52.8)	101 (10.2)	0	NA	7.3 (7.0–7.5)
Busselton Health Study, 1981 (25)	Adults in Busselton, Western Australia	2001	51 (18–90)	984 (49.2)	89 (4.4)	15 (0.7)	33 (1.6)	20 (19.5–20.0)
Birmingham Study, 1988 (21)	CDAs aged ≥60 y from primary care practice in Birmingham, UK	1107	69 (60–94)	628 (56.7)	92 (8.3)	0	29 (2.6)	10.2 (5.7–10.6)
Cardiovascular Health Study, 1989 (17)	CDAs with Medicare eligibility in 4 US communities	3017	71 (64–100)	1812 (60.1)	492 (16.3)	0	153 (5.1)	13.9 (8.6–16.4)
EPIC-Norfolk Study, 1995 (27)	Adults living in Norfolk, UK	12 709	58 (40–78)	6874 (54.1)	723 (5.7)	0	NA	13.4 (12.6–14.3)
Health, Aging, and Body Composition Study, 1997 (19)	CDAs with Medicare eligibility in 2 US communities	2677	74 (69–81)	1346 (50.3)	335 (12.5)	232 (8.7)	338 (12.6)	11.9 (7.5–12.2)
InCHIANTI Study, 1998 (37)	Adults aged 20–102 y living in Chianti geographic area, Italy	1099	71 (21–102)	612 (55.7)	33 (3.0)	21 (1.9)	NA	9.07 (8.1–9.2)
Leiden 85-plus Study, 1997 (15)	Adults aged 85 y living in Leiden, The Netherlands	493	85 (NA)	322 (65.3)	35 (7.1)	14 (2.8)	20 (4.1)	5.2 (2.5–8.6)
MrOS Study, 2000 (35)	Community-dwelling US men aged 65 y and older	1558	73 (65–99)	0	148 (9.5)	110 (7.1)	NA	12.0 (8.2–12.7)
Nagasaki Adult Health Study, 1984 (18)	Atomic bomb survivors in Nagasaki, Japan	2766	57 (38–92)	1688 (61.0)	424 (15.3)	39 (1.4)	6 (0.2)	13.0 (12.3–13.6)
Pisa cohort, 2000 (39)	Patients admitted to cardiology department in Pisa, Italy[d]	2922	63 (19–92)	935 (32.0)	227 (7.8)	12 (0.4)	0	2.5 (1.6–3.7)
PREVEND Study, 1997 (23)	Adults living in Groningen, The Netherlands	2562	46 (28–75)	1306 (51)	51 (2.0)	27 (1.1)	34 (1.3)	10.9 (10.6–11.1)
PROSPER trial, 1997 (40)	Trial on the benefits of pravastatin vs placebo in adults	5525	75 (69–83)	2801 (50.7)	446 (8.1)	211 (3.8)	264 (4.8)	3.3 (3.0–3.5)
Rotterdam Study, 1989 (10, 38)	Adults ≥55 y old living in Rotterdam, The Netherlands	1697	68 (55–93)	1036 (61.0)	104 (6.1)	30 (1.8)	NA	16.8 (11.1–18.9)
SHIP Study, 1997 (24)	Adults in West Pomerania, northeast of Germany	3118	47 (20–81)	1587 (50.9)	13 (0.4)	159 (5.1)	214 (6.9)	11.3 (10.6–11.8)
Whickham Survey, 1972 (29)	Adults living in and near Newcastle upon Tyne, UK	2448	46 (18–92)	1308 (54.4)	128 (5.2)	99 (4.0)	71 (2.9)	19 (15.0–20.0)
Overall		47 573	65 (18–102)	24 162 (50.8)	3451 (7.3)	1103 (2.3)	1224 (2.6)	11.6 (5.0–13.8)

Abbreviations: CDA, community-dwelling adult; IQR, interquartile range (25th-75th percentile); NA, not available.

[a] Participants younger than 18 years of age were not included.

[b] Participants with missing information on thyroid medication at baseline: Cardiovascular Health Study, 1; Health, Aging, and Body Composition Study, 7; Whickham Survey, 3; Rotterdam Study, 482; MrOS, 64.

[c] Participants with missing information on thyroid medication at follow-up: Birmingham, 1026; Whickham, 1489.

[d] Excluded patients with acute coronary syndrome or severe illness.

found a significantly increased risk of fatal stroke with a HR of 2.51 (95% CI, 1.42–4.44) in the younger group (p for interaction = 0.003) (Table 2). When looking at the incidence rate per 100 000 person-years for stroke events in the pooled dataset within each age group, we find 58 for the 18- to 49-year age group, 330 for the 50- to 64-year age group, 1127 for the 65- to 79-year age group, and 2991 for those 80 years and older. For fatal stroke, this was 11, 74, 370, and 1183 per 100 000 person-years for the respective age groups.

There was a nonsignificant pattern of increased risk of fatal stroke with higher TSH concentrations. In the age- and sex-adjusted analyses, the HR for fatal stroke was 1.18 (95% CI, 0.83–1.69) in participants with TSH levels between 4.5 and 6.9 mIU/L, 1.63 (95% CI, 1.09–2.43) for those with TSH levels between 7.0 and 9.9 mIU/L, and 1.69 (95% CI, 0.88–3.27) for those with TSH levels between 10.0 and 19.9 mIU/L, compared to the euthyroid group (p for trend 0.07). There was no observed difference by sex (p for interaction > 0.5).

Multivariable analyses, adjusting for sex, age, smoking, total cholesterol, systolic blood pressure, and history of diabetes yielded similar results, with the exception of fatal stroke analysis in the group between 50 and 65 years of age, which was attenuated after adjustment (Table 2). This was likely due to eliminating heterogeneity in this subgroup, with an I^2 of 29% in the age- and sex-adjusted analysis and 0% in the multivariable analysis.

Sensitivity analyses excluding several studies, excluding thyroid medication users, using only nonimputed data, additional adjustments, and other sensitivity analyses did not meaningfully affect the risk estimates (Supplemental Table 2). We found no evidence of publication bias, either with visual assessment of

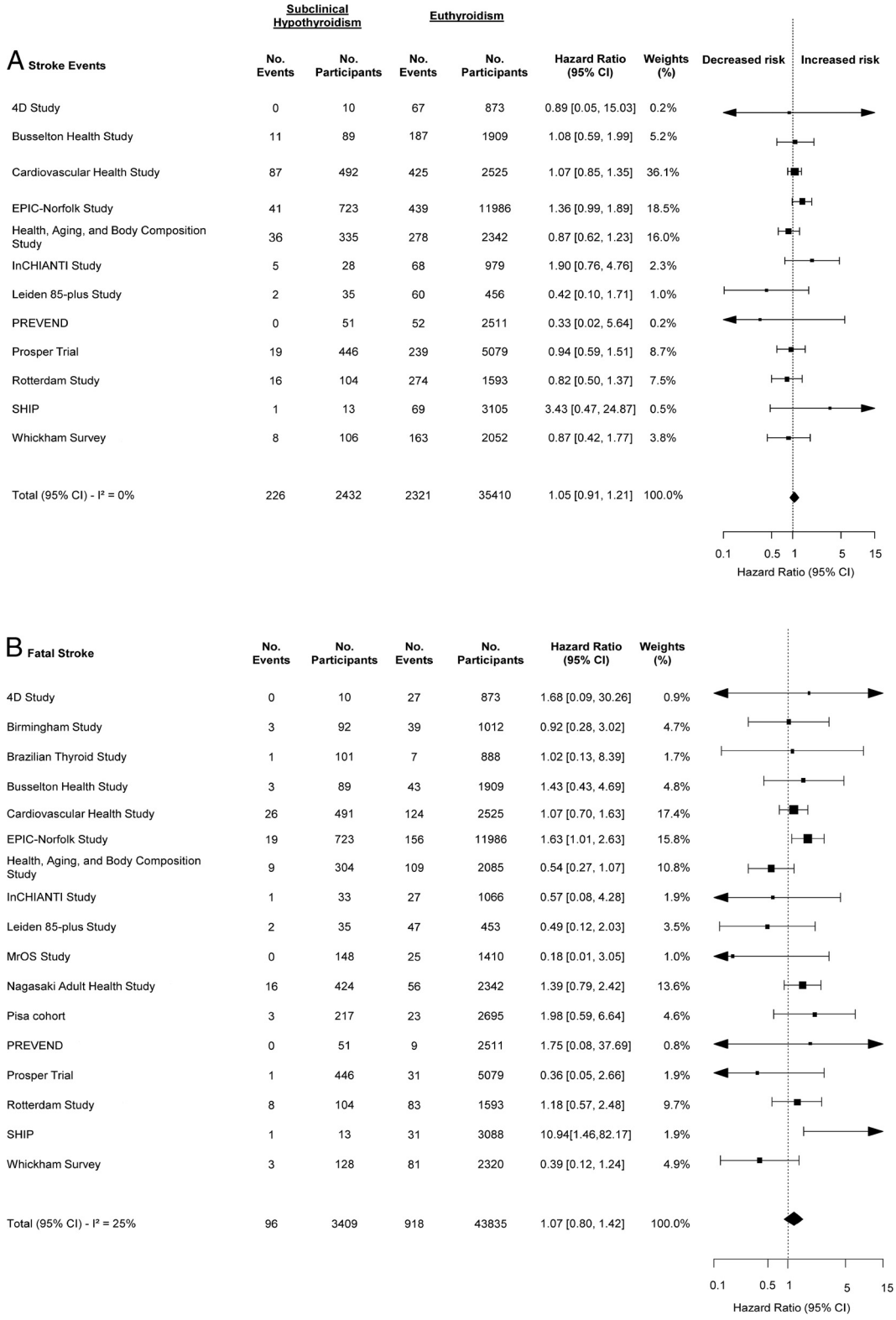

Figure 1. The risk of stroke events and fatal stroke in subclinical hypothyroidism vs euthyroidism. HRs and their 95% CIs are represented by squares. Sizes of data markers are proportional to the inverse of the variance of the HRs. A, Data for stroke events were available in 12 studies. A total of 387 participants were excluded from the analysis of stroke events due to missing follow-up data. B, Data for fatal strokes were available in 17 studies. A total of 329 participants were excluded from the analysis of fatal stroke due to missing cause of death.

Table 2. Stratified Analyses for the Associations Between Subclinical Hypothyroidism and the Risk of Stroke and Fatal Stroke

	Stroke Events[a]			Fatal Stroke[b]		
	No. of Events/Total Participants	Age- and Sex-Adjusted HR (95% CI)	Multivariable HR (95% CI)[c]	No. of Events/Total Participants	Age- and Sex-Adjusted HR (95% CI)	Multivariable HR (95% CI)[c]
Total Population	2547/37 842	1.05 (0.91, 1.21)	0.97 (0.77, 1.22)	1014/47 244	1.07 (0.80, 1.42)	1.11 (0.82, 1.50)
Men[d]	1177/17 644	1.12 (0.88, 1.42)	1.07 (0.90, 1.27)	452/23 238	1.19 (0.83, 1.70)	1.19 (0.82, 1.72)
Women[d]	1370/20 198	1.07 (0.90, 1.27)	1.17 (0.92, 1.49)	562/24 006	1.19 (0.86, 1.64)	1.24 (0.83, 1.84)
p for interaction		0.76	0.55		0.99	0.88
Age, y[e]						
18–49	64/8555	3.32 (1.25, 8.80)	3.34 (1.18, 9.46)	14/9879	4.22 (1.08, 16.55)	4.80 (1.03, 22.30)
50–64	381/9723	1.34 (0.65, 2.80)	1.34 (0.69, 2.62)	117/13 289	2.86 (1.31, 6.26)	1.99 (1.05, 3.74)
65–79	1803/17 611	1.00 (0.86, 1.18)	1.02 (0.87, 1.20)	698/21 460	1.07 (0.83, 1.39)	1.09 (0.82, 1.45)
≥80	299/1953	1.31 (0.79, 2.18)	1.43 (0.93, 2.18)	185/2616	1.23 (0.74, 2.04)	1.34 (0.75, 2.40)
p for trend		0.07	0.11		0.04	0.08
Age, y[e]						
18–64y	445/18 278	1.37 (0.71, 2.63)	1.46 (0.78, 2.73)	131/23 168	2.51 (1.42, 4.44)	2.29 (1.41, 3.74)
≥65y	2102/19 564	1.04 (0.90, 1.20)	1.03 (0.71, 1.49)	883/24 076	0.99 (0.81, 1.21)	1.04 (0.81, 1.32)
p for interaction		0.42	0.35		0.003	0.005
TSH, mIU/L						
0.45–4.49	2301/35 250	Reference	Reference	910/43 648	Reference	Reference
4.5–6.9	161/1799	1.01 (0.86, 1.19)	1.01 (0.85, 1.19)	72/2544	1.18 (0.83, 1.69)	1.09 (0.71, 1.67)
7.0–9.9	53/507	1.62 (0.89, 2.94)	1.68 (0.91, 3.09)	22/699	1.63 (1.09, 2.43)	1.65 (1.16, 2.33)
10.0–19.9	32/286	1.27 (0.90, 1.80)	1.26 (0.89, 1.79)	10/353	1.69 (0.88, 3.27)	1.79 (0.88, 3.63)
p for trend		0.05	0.05		0.07	0.05

[a] Data were available from 12 studies; 387 participants were excluded due to missing stroke event data.

[b] 329 participants were excluded due to missing data on cause of death.

[c] Adjusted for sex, age, systolic blood pressure, smoking, and prevalent diabetes at baseline. The Birmingham Study was excluded in this analysis because of a lack of data on cardiovascular risk factors.

[d] These analyses were not adjusted for sex.

[e] These HRs were adjusted for sex and age as continuous variables to avoid residual confounding within age strata.

age- and sex-adjusted funnel plots or with the Egger test for stroke events ($P = .67$) or fatal stroke ($P = .58$).

Discussion

In our IPD analysis of 47 573 participants from 17 prospective cohort studies, no overall effect of subclinical hypothyroidism was observed on the risk of stroke events or fatal stroke compared to euthyroidism in age- and sex-adjusted analyses. However, younger participants had an increased risk of stroke events and fatal stroke in subclinical hypothyroidism compared to euthyroidism. There was an increase in fatal stroke in those younger than 65 years and in participants with a TSH level of 7.0 to 9.9 mIU/L, but a nonsignificant p for trend (0.07). This is the first IPD analysis to investigate the association between subclinical hypothyroidism and stroke. We are also the first to detect differences by age in associations between subclinical hypothyroidism and a clinical outcome in an IPD analysis.

The mechanisms by which subclinical hypothyroidism increases the risk of stroke, as found in specific subgroups, could be explained by the increased prevalence of cardiovascular risk factors in those with subclinical hypothyroidism. Thyroid hormones have direct effects on the cardiovascular system and are known to decrease systemic vascular resistance (45) and alter systolic and diastolic cardiac function (46). Thyroid hormone deficiency increases the risk of several cardiovascular risk factors including hypertension (47), dyslipidemia (48), and atherosclerosis (49). These changes have also been observed in subclinical thyroid dysfunction (10, 50). However, our multivariable IPD analyses yielded similar results to the age- and sex-adjusted analyses. Adjusting for smoking, total cholesterol, systolic blood pressure, and diabetes only slightly changed the risk estimates in the age-stratified analysis of fatal stroke for participants between 50 and 65 years old. The fact that adjustment for traditional cardiovascular risk factors did not substantially alter risk estimates suggests an independent association of subclinical hypothyroidism on the risk of stroke and also indicates that total cholesterol, systolic blood pressure, and diabetes are not relevant factors mediating the hypothetical pathway between subclinical hypothyroidism and

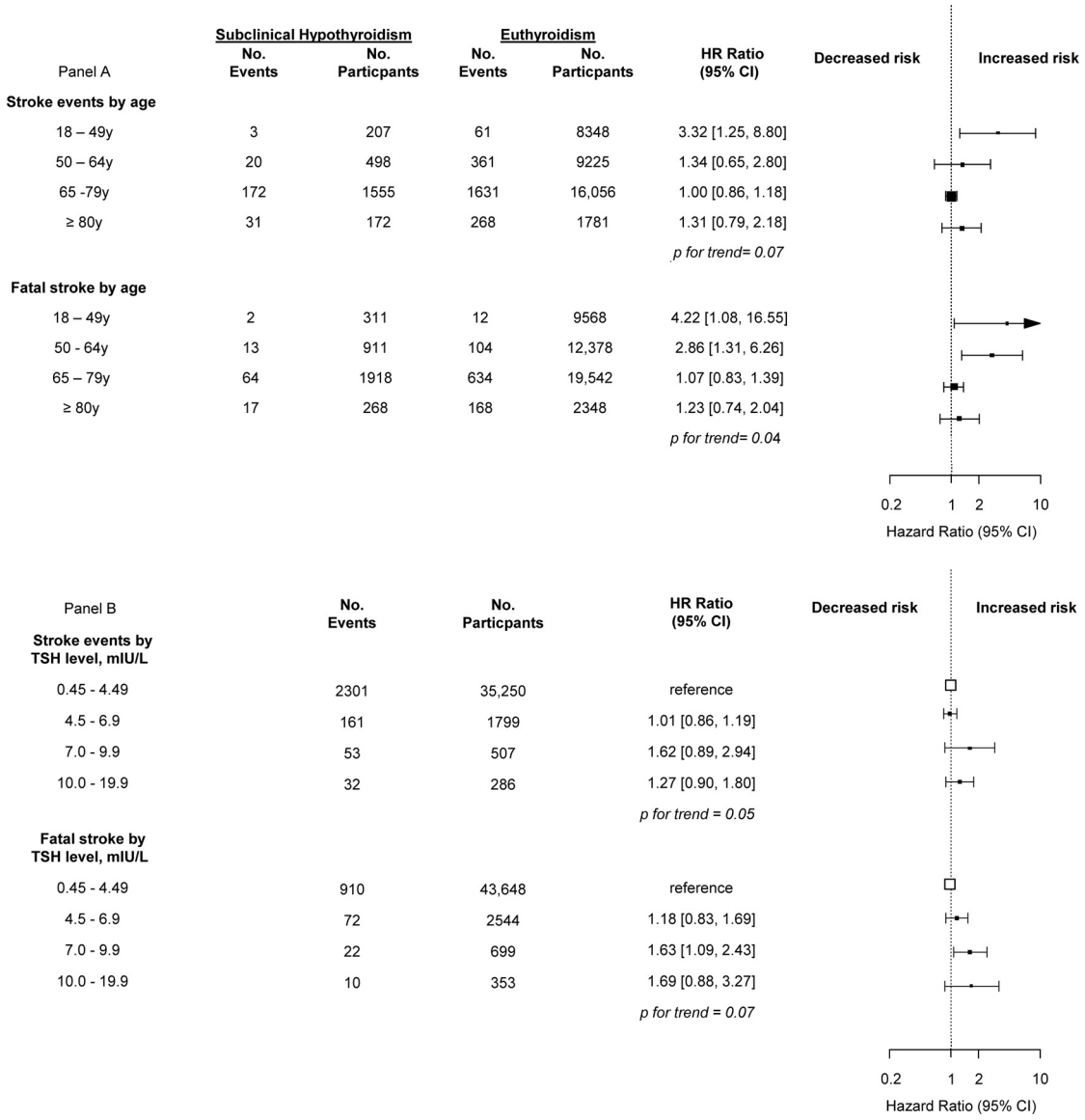

Figure 2. HRs for stroke events and fatal stroke for subclinical hypothyroidism stratified by age vs euthyroidism (A) and according to elevated TSH categories (B). HRs and their 95% CIs are represented by squares. Sizes of data markers are proportional to the inverse of the variance of the HRs. Unfilled squares indicate the reference categories. For the analysis stratified by age, HRs for stroke events and fatal stroke were adjusted for sex and age as a continuous variable to avoid residual confounding within age strata. Data for stroke events were available in 12 studies. A total of 387 participants were excluded from the analysis of stroke events due to missing stroke event data. Data for fatal strokes were available in 17 studies. A total of 329 participants were excluded from the analysis of fatal stroke due to missing cause of death.

stroke. Another explanation might be that this is due to some unmeasured confounders or mediators.

Various abnormalities in the hemostatic system have been reported in overt (51, 52) and subclinical hypothyroidism (53–55). Alterations in coagulability and the fibrinolytic system have been linked to a high risk of CVD (56). This might also be one of the mechanisms that play a role in the increased risk of stroke in subclinical hypothyroidism. We were not able to discriminate between hemorrhagic and ischemic stroke in the current study because most cohorts did not collect these data. Another pathway linked with both thyroid function and risk of stroke is atrial fibrillation (26). This, however, seems unlikely because atrial fibrillation is linked to overt and subclinical hyperthyroidism and not to hypothyroidism (26). The exact mechanistic relationship between subclinical hypothyroidism and the risk of stroke still remains to be determined.

In our study, younger individuals with subclinical hypothyroidism had a higher risk of stroke events and fatal stroke compared with euthyroid subjects within the same age groups. Although a higher risk in those younger than 65 years of age has previously been reported in a meta-analysis of published data studying the association between subclinical thyroid disease and coronary heart disease (57), this was not confirmed by an IPD analysis

investigating the same association (12). Several population-based studies and published data meta-analysis found an association between subclinical hypothyroidism and various clinical outcomes, including self-reported health (58), ischemic heart disease (14, 18, 29, 57), and cognition (15) when including younger age groups but not in older populations. However, these differences in association by age have not been observed in IPD analyses prior to ours.

In our IPD analysis, the relationship between subclinical hypothyroidism and the risk of stroke seen in younger individuals does not seem to hold in populations 65 years and older. This seems counterintuitive because both the prevalence and incidence of subclinical hypothyroidism and stroke are higher in the elderly than in younger populations. An explanation for the absence of the association in elderly subjects could be that adverse outcomes of subclinical hypothyroidism (eg, hyperlipidemia) are leveled out in this particular group due to the slowing of metabolic rate and energy expenditure (59), reduced sensitivity to adrenergic stimulation (60), or other counterbalancing protective factors. Also, differences in stroke etiology in younger vs older individuals could explain the difference in risk estimates by age group. For example, stroke in younger adults is more often hemorrhagic compared to older individuals (61). Subclinical and overt hypothyroidism are linked to hypocoagulability (51) and could through this pathway have a stronger effect on younger adults than on the elderly. There might also be the possibility of competing risk of events in the elderly. However, this rarely leads to meaningful changes in relative risk estimates of the HR (62). Another possible explanation for the different risks across age groups might be a changed hypothalamus-pituitary-thyroid set point in the elderly, leading to higher TSH levels (63, 64). In this case, subclinical hypothyroidism, defined as a TSH >4.5 mIU/L, may not reflect thyroidal status as well as in younger individuals (65–67), and subclinical hypothyroidism and stroke would exist simultaneously rather than have a causal relation in those older than 65 years of age. It is debated whether age-specific reference ranges are needed to define the normal range and herewith also the altered state of thyroid function. Some studies have found relevant reclassification of thyroid status by applying age-specific reference ranges of TSH (68), whereas others have not (69). The question remains whether the definition of the normal range should be based on age-specific biochemical cutoffs or instead be based on the risk of clinical adverse events associated with these cutoffs. The findings of our study suggest that for older subjects a TSH cutoff higher than 4.5 mIU/L could be applied, whereas this cutoff might be too high for younger individuals. However, further studies are needed to determine the risks and benefits of redefining the cutoffs of thyroid function.

We found a higher risk of fatal stroke in a subset of subclinically hypothyroid individuals with TSH levels between 7.0 and 9.9 mIU/L, when compared to individuals with values within the TSH reference range. We were not able to demonstrate an association for the subgroup with a TSH level between 10.0 and 19.9 mIU/L, which is probably due to a lack of power because the point estimate for fatal stroke was higher than for TSH levels between 7.0 and 9.9 mIU/ml, suggesting a dose-response relationship.

The strength of our study is that we were able to perform an IPD analysis including over 47 000 participants from 17 cohort studies, based on published and unpublished data. We did an extensive literature search and included all available published data on the association between subclinical hypothyroidism and the risk of stroke and fatal stroke. Furthermore, we were able to find additional cohorts with unpublished longitudinal data with information on thyroid function and stroke outcomes. One of the advantages of performing an IPD analysis is that it enables the standardization of the definition of exposures and covariates used for the time-to-event analyses, allowing a more uniform interpretation. Although we found similar overall results in this IPD analysis compared to the previous study-level meta-analysis (16), we did observe additional important findings in subgroups that were not detected by meta-analyzing the aggregate data. This highlights the strength of an IPD analysis because it provides a better opportunity for subgroup and sensitivity analyses.

Despite the large number of participants, we had limited power mainly for the stratified analyses. Power calculations showed that our study had a statistical power of 80% to detect a HR of 1.57 for stroke events and a HR of 1.61 for stroke mortality. The power was especially limited in the age subgroup analyses under 50 where the number of events was decreased, reflected in the wide CIs. There were also limited numbers of events in those with TSH levels between 10.0 and 19.9 mIU/L. Information on thyroid medication use during follow-up, which could alter risk over time, was not available for some cohorts. We were unable to perform analyses stratified by type of stroke (ischemic vs hemorrhagic) due to a limited number of events in each stratum or by race due to having few nonwhite participants. Furthermore, thyroid function was determined only at baseline in most cohorts, and therefore it was not possible to take the evolution of thyroid dysfunction over time into account. Because a number of participants with mildly elevated TSH levels will normalize in the course of time, a second measurement of thyroid function would have enabled us to spe-

cifically investigate participants with persistent subclinical hypothyroidism, where perhaps the effects are more pronounced.

In summary we found no association between subclinical hypothyroidism and overall risk of stroke events or fatal stroke. In stratified analyses, younger participants, particularly those under the age of 50 years, had increased stroke risk, although the number of events was small. Those with TSH of 7.0–9.9 mIU/L also had an increased risk of fatal stroke compared to their euthyroid counterparts. Our data are reassuring for those over the age of 65 years and those with TSH levels between 4.5 and 6.9 mIU/L, who represent most participants with subclinical hypothyroidism. Whether treatment of subclinical hypothyroidism will result in a decrease of the risk of stroke in younger subjects or those with higher TSH levels needs to be answered by a sufficiently powered randomized clinical trial.

Acknowledgments

We gratefully acknowledge the contribution of all studies, study participants, the staff from the all participating studies, and the participating general practitioners, pharmacists, and other health care professionals. We also thank the Bari study for agreeing to participate and providing us with individual participant data. We express our gratitude to Professor Eric Vittinghoff, PhD (Division of Biostatistics, Department of Epidemiology and Biostatics, University of California, San Francisco) for statistical assistance and Dr Joost van Rosmalen, PhD (Department of Biostatistics, Erasmus Medical Center, Rotterdam) for providing support in statistical analyses. We also thank Wichor M. Bramer (Medical Library, Erasmus Medical Center, Rotterdam) for the important contribution to the literature search.

Address all correspondence and requests for reprints to: R. P. Peeters, MD, PhD, Rotterdam Thyroid Center, Department of Internal Medicine, Erasmus University Medical Center, Room Ee 500, PO Box 2040, 3000 CA Rotterdam, The Netherlands. E-mail: r.peeters@erasmusmc.nl.

This study was supported by an Erasmus MC Medical Research Advisory Committee grant and ZonMW TOP Grant 21.12.044 (to R.P.P.) . R.P.P. has received lecture and consultancy fees from Genzyme B.V. The Thyroid Studies Collaboration is supported by grants from the Swiss National Science Foundation (320030-138267 and 320030-150025; to N.R.).

The study was supported by an Erasmus MC MRACE grant and a ZonMW TOPgrant (21.12.044) to Dr. R. P. Peeters. Dr. R.P. Peeters has received lecture and consultancy fees from Genzyme B.V. The Thyroid Studies Collaboration is supported by a grant from the Swiss National Science Foundation (SNSF 320030-138267 and 320030-150025 to Prof. N. Rodondi). Dr. T-H Collet's research is supported by grants from the Swiss National Science Foundation (PBLAP3-145870) and the Swiss Foundation for Grants in Biology and Medicine (P3SMP3-155318). The Cardiovascular Health Study (CHS) was supported by R01AG032317 and K24AG042765 from the National Institute on Aging (NIA), contracts HHSN268201200036C, HHSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, and grant HL080295 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided by AG023629,19 from the NIA. A full list of principal CHS investigators and institutions can be found at CH NHLBI.org. The Health ABC Study was supported by National Institute on Aging (NIA) Contracts N01-AG-6-2101; N01-AG-6-2103; N01-AG-6-2106; NIA grant R01-AG028050, and NINR grant R01-NR012459. SHIP data collection and analysis were supported by the Research Network of Community Medicine and the German Research Foundation (DFG Vo 955/12-1). The Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan is a public interest foundation funded by the Japanese Ministry of Health, Labour and Welfare (MHLW) and the US Department of Energy (DOE). The research was also funded in part through DOE award DE-HS0000031 to the National Academy of Sciences. The Brazilian Thyroid Study was supported by an unrestricted grant from the Sao Paulo State Research Foundation (Fundação de Amaparo a Pesquisa do Estado de Sao Paulo, FAPESP, grant 6/59737-9 to Dr Maciel). The Dutch Kidney Foundation supported the infrastructure of the PREVEND program from 1997 to 2003 (Grant E.033). The University Medical Center Groningen supported the infrastructure from 2003 to 2006. Dade Behring, Ausam, Roche, and Abbott financed laboratory equipment and reagents by which various laboratory determinations could be performed. The Dutch Heart Foundation supported studies on lipid metabolism (Grant 2001-005). The Osteoporotic Fractures in Men (MrOS) Study is supported by National Institutes of Health funding. The following institutes provide support: the National Institute on Aging (NIA), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Center for Advancing Translational Sciences (NCATS), and NIH Roadmap for Medical Research under the following grant numbers: U01 AG027810, U01 AG042124, U01 AG042139, U01 AG042140, U01 AG042143, U01 AG042145, U01 AG042168, U01 AR066160, and UL1 TR000128.

Disclosure Summary: The authors have nothing to disclose.

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. **Gharib H, Tuttle RM, Baskin HJ, Fish LH, Singer PA, McDermott MT.** Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society. *J Clin Endocrinol Metab*. 2005;90:581–585; discussion 586–587.
3. **Helfand M, U.S. Preventive Services Task Force.** Screening for subclinical thyroid dysfunction in nonpregnant adults: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2004;140:128–141.
4. **Aghini-Lombardi F, Antonangeli L, Martino E, et al.** The spectrum of thyroid disorders in an iodine-deficient community: the Pescopagano survey. *J Clin Endocrinol Metab*. 1999;84:561–566.
5. **Aoki Y, Belin RM, Clickner R, Jeffries R, Phillips L, Mahaffey KR.** Serum TSH and total T4 in the United States population and their association with participant characteristics: National Health and

Nutrition Examination Survey (NHANES 1999–2002). *Thyroid*. 2007;17:1211–1223.
6. **Canaris GJ, Manowitz NR, Mayor G, Ridgway EC.** The Colorado thyroid disease prevalence study. *Arch Intern Med*. 2000;160:526–534.
7. **Teng W, Shan Z, Teng X, et al.** Effect of iodine intake on thyroid diseases in China. *N Engl J Med*. 2006;354:2783–2793.
8. **Bauer DC, Ettinger B, Browner WS.** Thyroid functions and serum lipids in older women: a population-based study. *Am J Med*. 1998;104:546–551.
9. **Biondi B.** Cardiovascular effects of mild hypothyroidism. *Thyroid*. 2007;17:625–630.
10. **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.
11. **Gao N, Zhang W, Zhang YZ, Yang Q, Chen SH.** Carotid intima-media thickness in patients with subclinical hypothyroidism: a meta-analysis. *Atherosclerosis*. 2013;227:18–25.
12. **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.
13. **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.
14. **Razvi S, Shakoor A, Vanderpump M, Weaver JU, Pearce SH.** The influence of age on the relationship between subclinical hypothyroidism and ischemic heart disease: a metaanalysis. *J Clin Endocrinol Metab*. 2008;93:2998–3007.
15. **Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frölich M, Westendorp RG.** Thyroid status, disability and cognitive function, and survival in old age. *JAMA*. 2004;292:2591–2599.
16. **Chaker L, Baumgartner C, Ikram MA, et al.** Subclinical thyroid dysfunction and the risk of stroke: a systematic review and meta-analysis. *Eur J Epidemiol*. 2014;29:791–800.
17. **Cappola AR, Fried LP, Arnold AM, et al.** Thyroid status, cardiovascular risk, and mortality in older adults. *JAMA*. 2006;295:1033–1041.
18. **Imaizumi M, Akahoshi M, Ichimaru S, et al.** Risk for ischemic heart disease and all-cause mortality in subclinical hypothyroidism. *J Clin Endocrinol Metab*. 2004;89:3365–3370.
19. **Rodondi N, Newman AB, Vittinghoff E, et al.** Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. *Arch Intern Med*. 2005;165:2460–2466.
20. **Drechsler C, Schneider A, Gutjahr-Lengsfeld L, et al.** Thyroid function, cardiovascular events, and mortality in diabetic hemodialysis patients. *Am J Kidney Dis*. 2014;63:988–996.
21. **Parle JV, Maisonneuve P, Sheppard MC, Boyle P, Franklyn JA.** Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. *Lancet*. 2001;358:861–865.
22. **Schultz M, Kistorp C, Raymond I, et al.** Cardiovascular events in thyroid disease: a population based, prospective study. *Horm Metab Res*. 2011;43:653–659.
23. **Hillege HL, Janssen WM, Bak AA, et al.** Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. *J Intern Med*. 2001;249:519–526.
24. **Völzke H, Alte D, Schmidt CO, et al.** Cohort profile: the study of health in Pomerania. *Int J Epidemiol*. 2011;40:294–307.
25. **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.
26. **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.
27. **Boekholdt SM, Titan SM, Wiersinga WM, et al.** Initial thyroid status and cardiovascular risk factors: the EPIC-Norfolk prospective population study. *Clin Endocrinol (Oxf)*. 2010;72:404–410.
28. **Nicoloff JT, Spencer CA.** Clinical review 12: the use and misuse of the sensitive thyrotropin assays. *J Clin Endocrinol Metab*. 1990;71:553–558.
29. **Razvi S, Weaver JU, Vanderpump MP, Pearce SH.** The incidence of ischemic heart disease and mortality in people with subclinical hypothyroidism: reanalysis of the Whickham Survey cohort. *J Clin Endocrinol Metab*. 2010;95:1734–1740.
30. **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.
31. **DerSimonian R, Laird N.** Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
32. **Higgins JP, Thompson SG.** Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539–1558.
33. **Firth D.** Bias reduction of maximum likelihood estimates. *Biometrika*. 1993;80:27–38.
34. **Heinze G, Schemper M.** A solution to the problem of monotone likelihood in Cox regression. *Biometrics*. 2001;57:114–119.
35. **Waring AC, Harrison S, Samuels MH, et al.** Thyroid function and mortality in older men: a prospective study. *J Clin Endocrinol Metab*. 2012;97:862–870.
36. **Egger M, Davey Smith G, Schneider M, Minder C.** Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634.
37. **Ferrucci L, Bandinelli S, Benvenuti E, et al.** Subsystems contributing to the decline in ability to walk: bridging the gap between epidemiology and geriatric practice in the InCHIANTI study. *J Am Geriatr Soc*. 2000;48:1618–1625.
38. **Hofman A, Darwish Murad S, van Duijn CM, et al.** The Rotterdam Study: 2014 objectives and design update. *Eur J Epidemiol*. 2013;28:889–926.
39. **Iervasi G, Molinaro S, Landi P, et al.** Association between increased mortality and mild thyroid dysfunction in cardiac patients. *Arch Intern Med*. 2007;167:1526–1532.
40. **Nanchen D, Gussekloo J, Westendorp RG, et al.** Subclinical thyroid dysfunction and the risk of heart failure in older persons at high cardiovascular risk. *J Clin Endocrinol Metab*. 2012;97:852–861.
41. **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.
42. **Iacoviello M, Guida P, Guastamacchia E, et al.** Prognostic role of sub-clinical hypothyroidism in chronic heart failure outpatients. *Curr Pharm Des*. 2008;14:2686–2692.
43. **Blank JB, Cawthon PM, Carrion-Petersen ML, et al.** Overview of recruitment for the osteoporotic fractures in men study (MrOS). *Contemp Clin Trials*. 2005;26:557–568.
44. **Orwoll E, Blank JB, Barrett-Connor E, et al.** Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study–a large observational study of the determinants of fracture in older men. *Contemp Clin Trials*. 2005;26:569–585.
45. **Klein I, Ojamaa K.** Thyroid hormone: targeting the vascular smooth muscle cell. *Circ Res*. 2001;88:260–261.
46. **Klein I, Ojamaa K.** Thyroid hormone and the cardiovascular system. *N Engl J Med*. 2001;344:501–509.
47. **Nagasaki T, Inaba M, Kumeda Y, et al.** Increased pulse wave velocity in subclinical hypothyroidism. *J Clin Endocrinol Metab*. 2006;91:154–158.
48. **Duntas LH.** Thyroid disease and lipids. *Thyroid*. 2002;12:287–293.
49. **Cappola AR, Ladenson PW.** Hypothyroidism and atherosclerosis. *J Clin Endocrinol Metab*. 2003;88:2438–2444.
50. **Biondi B, Cooper DS.** The clinical significance of subclinical thyroid dysfunction. *Endocr Rev*. 2008;29:76–131.
51. **Erem C.** Coagulation and fibrinolysis in thyroid dysfunction. *Endocrine*. 2009;36:110–118.

52. **Erem C, Kavgaci H, Ersöz HO, et al.** Blood coagulation and fibrinolytic activity in hypothyroidism. *Int J Clin Pract*. 2003;57:78–81.
53. **Guldiken S, Demir M, Turgut B, Altun BU, Arikan E, Kara M.** Global fibrinolytic capacity in patients with subclinical hypothyroidism. *Endocr J*. 2005;52:363–367.
54. **Jorde R, Figenschau Y, Hansen JB.** Haemostatic function in subjects with mild subclinical hypothyroidism. The Tromsø study. *Thromb Haemost*. 2006;95:750–751.
55. **Cantürk Z, Cetinarslan B, Tarkun I, Cantürk NZ, Ozden M, Duman C.** Hemostatic system as a risk factor for cardiovascular disease in women with subclinical hypothyroidism. *Thyroid*. 2003;13:971–977.
56. **Wiman B, Andersson T, Hallqvist J, Reuterwall C, Ahlbom A, de-Faire U.** Plasma levels of tissue plasminogen activator/plasminogen activator inhibitor-1 complex and von Willebrand factor are significant risk markers for recurrent myocardial infarction in the Stockholm Heart Epidemiology Program (SHEEP) study. *Arterioscler Thromb Vasc Biol*. 2000;20:2019–2023.
57. **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.
58. **Razvi S, Ingoe LE, McMillan CV, Weaver JU.** Health status in patients with sub-clinical hypothyroidism. *Eur J Endocrinol*. 2005;152:713–717.
59. **Kim B.** Thyroid hormone as a determinant of energy expenditure and the basal metabolic rate. *Thyroid*. 2008;18:141–144.
60. **Silva JE, Bianco SD.** Thyroid-adrenergic interactions: physiological and clinical implications. *Thyroid*. 2008;18:157–165.
61. **Singhal AB, Biller J, Elkind MS, et al.** Recognition and management of stroke in young adults and adolescents. *Neurology*. 2013;81:1089–1097.
62. **Putter H, Fiocco M, Geskus RB.** Tutorial in biostatistics: competing risks and multi-state models. *Stat Med*. 2007;26:2389–2430.
63. **Surks MI, Hollowell JG.** Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. *J Clin Endocrinol Metab*. 2007;92:4575–4582.
64. **Pearce SHS, Brabant G, Duntas LH, et al.** 2013 ETA guideline: management of subclinical hypothyroidism. *Eur Thyroid J*. 2013;2:215–228.
65. **Lewis GF, Alessi CA, Imperial JG, Refetoff S.** Low serum free thyroxine index in ambulating elderly is due to a resetting of the threshold of thyrotropin feedback suppression. *J Clin Endocrinol Metab*. 1991;73:843–849.
66. **Bremner AP, Feddema P, Leedman PJ, et al.** Age-related changes in thyroid function: a longitudinal study of a community-based cohort. *J Clin Endocrinol Metab*. 2012;97:1554–1562.
67. **Waring AC, Arnold AM, Newman AB, Bùzková 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.
68. **Vadiveloo T, Donnan PT, Murphy MJ, Leese GP.** Age- and gender-specific TSH reference intervals in people with no obvious thyroid disease in Tayside, Scotland: the Thyroid Epidemiology, Audit, and Research Study (TEARS). *J Clin Endocrinol Metab*. 2013;98:1147–1153.
69. **Kahapola-Arachchige KM, Hadlow N, Wardrop R, Lim EM, Walsh JP.** Age-specific TSH reference ranges have minimal impact on the diagnosis of thyroid dysfunction. *Clin Endocrinol (Oxf)*. 2012;77:773–779.