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

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Abstract

Objective 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 Unpublished studies were identified through the Thyroid Studies Collaboration.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 (IPD) on thyroid function and stroke outcome. Euthyroidism was defined as thyrotropin (TSH) levels 0.45-4.49 mIU/L, subclinical hypothyroidism as TSH levels 4.5-19.9 mIU/L with normal thyroxin levels.

Data Extraction and Synthesis We collected IPD on 47,573 adults (3451 subclinical hypothyroidism) from 17 cohorts, followed-up 1972-2014 (489,192 person-years). Age- and sex-adjusted pooled hazard ratio (HR) for participants with subclinical hypothyroidism compared to euthyroidism was 1.05 (95% CI, 0.91-1.21) for stroke events (combined fatal and non-fatal 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 (HR 1.00, 95% CI, 0.86-1.18) or ≥80 years (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.

Introduction

Subclinical hypothyroidism is defined as an elevated thyrotropin (TSH) level above the upper limit of the reference range with a free thyroxin (FT4) value that is normal (1-3). It has a prevalence varying between 4-14% 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 (IMT) (11). Furthermore, the association between subclinical hypothyroidism and risk of clinical 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 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 pre-specified 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 the 18th of November 2013 (**Supporting Information**). We included publications from longitudinal studies that measured at least TSH and (F)T4 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 (TSC), 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 1 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), history of diabetes, smoking and previous cerebrovascular disease. We also collected available information on medication use (thyroid hormone replacement, anti-thyroid, lipid-lowering and

anti-hypertensive therapy), demographic information (age, sex and ethnicity), anthropometric measurements (height and weight) and the outcome. Primary outcome measures were stroke events (fatal and non-fatal) and fatal stroke. Stroke was defined according to World Health Organization (WHO) 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 in order 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 (free) T4 concentration. Euthyroidism was defined as TSH level between 0.45 and 4.49 mIU/L. Most studies used a third-generation TSH radioimmunoassay, 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 subclinical hypothyroidism, as previously described (12, 29). In addition the Whickham Survey was the only study to perform total T4 assays (29); the remainder performed free T4 (FT4) assays.

For (F)T4 values, we used site- and method-dependent cutoffs, as 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 (F)T4 values (n=3967). When (F)T4 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. Armonk, NY: 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 (R-project, Institute for Statistics and Mathematics, R Core Team (2013), Vienna, Austria, version 3.0.2). 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 the primary analysis because 1) covariates used in the multivariable analyses could also be considered as mediators 2) it includes all studies in contrast to the multivariable analysis that does not include the Birmingham cohort.

In order to identify populations at risk and possible sources of heterogeneity, we conducted pre-defined subgroup and sensitivity analyses. We performed stratified analyses by age, sex and

182 degree of TSH elevation. Based on expert reviews (1, 3) and following our previous approach
183 (12, 13) we stratified subclinical hypothyroidism into the following TSH categories: 4.5-6.9
184 mIU/L, 7.0-9.9 mIU/L and 10.0-19.9 mIU/L. If a study did not have an event in the (stratified)
185 study-specific analysis, we used Firth's penalized maximum likelihood bias reduction method for
186 the Cox model (33, 34) to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).
187 We conducted the following sensitivity analyses: 1) excluding three (20, 23, 35) studies that did
188 not have stroke events (non-fatal and fatal) in the subclinical hypothyroidism group 2) excluding
189 participants who had thyroid-function altering medication at baseline and during follow-up 3)
190 excluding studies that included transient ischemic attack (TIA) as a stroke event 4) excluding
191 participants with a history of stroke 5) excluding participants with missing (F)T4 levels 6) using
192 only unimputed data 7) cohorts with potential co-morbidities and 8) including the published risk
193 estimates of the study that declined to participate in the meta-analysis (22). We assessed age- and
194 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, 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 non-fatal stroke, contributing to the stroke events analysis among 37,842 participants. During follow-up 2547 stroke events occurred and 1014 participants had a fatal stroke.

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 18-49 year age group with subclinical hypothyroidism compared to euthyroidism, but the number of events was small (Table 2, Figure 2). For the 50-64 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 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 incidence rate per 100,000 person-years for stroke events in the pooled dataset within each age group we find 58 for the18-49 year age group, 330 for the 50-64 year group, 1127 for the 65-79 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 non-significant 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 age 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 non-imputed 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 age- and sex-adjusted funnel plots or with the Egger test for stroke events ($p = 0.67$) or fatal stroke ($p = 0.58$).

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 non-significant 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 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 haemorragic and ischemic stroke in the current study as 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 as 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 of 65 years and older. This seems counterintuitive as both the prevalence and incidence of subclinical hypothyroidism and stroke are higher in elderly than in younger populations. An explanation for the absence of the association in elderly subjects could be that adverse outcomes of subclinical hypothyroidism (e.g. hyperlipidemia) are leveled out in this particular group due to 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 versus 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 rather 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 hazard ratio (62). Another possible explanation for the different risks across age groups might be a changed hypothalamus-pituitary-thyroid set point in elderly, leading to higher TSH levels (63, 64). In this case subclinical hypothyroidism, defined with 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), while others have not (69). The question remains whether the definition of the normal range should be based on age-specific biochemical cut-offs or rather

based on risk of clinical adverse events associated with these cut-offs. The findings of our study suggest that for older subjects a TSH cut-off higher than 4.5 ImU/L could be applied, while this cut-off might be too high for younger individuals. However, further studies are needed to determine the risks and benefits of redefining the cut-offs 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 lack of power, as 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 strengths 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, as 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 limited especially in the age subgroup analyses under 50 where the number of events was decreased, reflected in the wide confidence intervals. 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 limited number of events in each stratum or by race due to having few non-white 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. As 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 specifically 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, though 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 the majority of participants with subclinical hypothyroidism. Whether treatment of subclinical hypothyroidism will result in a decrease of risk of stroke in younger subjects or those with higher TSH levels needs to be answered by a sufficiently powered randomized clinical trial.

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Legend of Figures

Figure 1. **The Risk of Stroke Events and Fatal Stroke in Subclinical Hypothyroidism versus Euthyroidism[a]**

[a] Hazard ratios (HRs) and their 95% confidence intervals (CIs) are represented by squares. Sizes of data markers are proportional to the inverse of the variance of the hazard ratios.

[b] Data for stroke events were available in 12 studies. Three hundred eighty-seven participants were excluded from the analysis of stroke event due to missing follow-up data.

[c] Data for fatal stroke were available in 17 studies. Three hundred twenty-nine participants were excluded from the analysis of fatal stroke, due to missing cause of death.

Figure 2. **Hazard Ratios (HRs) for Stroke Events and Fatal Stroke for Subclinical Hypothyroidism Stratified by Age vs Euthyroidism and According to Elevated Thyroid–Stimulating Hormone (TSH) Categories[a]**

[a] Hazard ratios (HRs) and their 95% confidence intervals (CIs) are represented by squares. Sizes of data markers are proportional to the inverse of the variance of the hazard ratios. 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.

[b] Data for stroke events were available in 12 studies. Three hundred eighty-seven participants were excluded from the analysis of stroke event due to missing stroke event data.

[c] Data for fatal stroke were available in 17 studies. Three hundred twenty-nine participants were excluded from the analysis of fatal stroke, due to missing cause of death.

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

Study, Start year	Description of Study Sample	No.	Median Age (Range), years[a]	Women No. (%)	Subclinical Hypothyroidism No. (%)	Thyroid Medication No. (%) at baseline[b]	Thyroid Medication No. (%) follow up[c]	Median Duration (IQR), years
4D Study[20], 1998	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[41], 1999	Adults from 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[25], 1981	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[21], 1988	CDA's aged ≥ 60 y from primary care practice in Birmingham, England	1107	69 (60-94)	628 (56.7)	92 (8.3)	0	29 (2.6)	10.2 (5.7-10.6)
Cardiovascular Health Study[17], 1989	CDA's 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[27], 1995	Adults living in Norfolk, England	12709	58 (40-78)	6874 (54.1)	723 (5.7)	0	NA	13.4 (12.6-14.3)
Health, Aging, and Body Composition Study[19], 1997	CDA's 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[37], 1998	Adults aged 20-102 years 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[15], 1997	Adults aged 85 years 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[35], 2000	Community-dwelling U.S. men aged 65 years and older	1558	73 (65-99)	0	148 (9.5)	110 (7.1)	NA	12.0 (8.2-12.7)

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

Study, Start year	Description of Study Sample	No.	Median Age (Range), years[a]	Women No. (%)	Subclinical Hypothyroidism No. (%)	Thyroid Medication No. (%) at baseline[b]	Thyroid Medication No. (%) follow up[c]	Median Duration (IQR), years
Nagasaki Adult Health Study[18], 1984	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[39], 2000	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[23], 1997	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[40], 1997	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[10, 38], 1989	Adults ≥55 years 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[24], 1997	Adults in West Pomerania, North-East 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[29], 1972	Adults living in & near Newcastle upon Tyne, England	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: CHS 1, HABC 7, Whickham 3, RS 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

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. events/ Total participants	**Age & sex adjusted HR (95% CI)**	**Multivariable[c] HR (95% CI)**	**No. events/ Total participants**	**Age & sex adjusted HR (95% CI)**	**Multivariable[c] HR (95% CI)**
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[e]	18 – 49y	64/8555	3.32 (1.25, 8.80)	3.34 (1.18, 9.46)	14 / 9,879	4.22 (1.08, 16.55)	4.80 (1.03, 22.30)
	50 – 64y	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 -79y	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)	185/2,616	1.23 (0.74, 2.04)	1.34 (0.75, 2.40)
	p for trend		*0.07*	*0.11*		*0.04*	*0.08*
Age[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*

Abbreviations: CI, confidence interval; HR, hazard ratio; TSH, thyroid-stimulating hormone.

[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 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 variable to avoid residual confounding within age strata.