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# Thyroid antibody status, subclinical hypothyroidism, and the risk of coronary heart disease: an individual participant data analysis

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

Abstract: 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.

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# Thyroid antibody status, subclinical hypothyroidism and the risk of coronary heart disease - An individual participant data analysis

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## Abstract

### Context

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

### Objective

To compare the CHD risk of subclinical hypothyroidism with and without thyroid peroxidase antibodies (TPOAb).

### Data sources and Study selection

MEDLINE and EMBASE search from 1950 to 2011 for prospective cohorts, reporting baseline thyroid function, antibodies and CHD outcomes.

### Data extraction

Individual data of 38,274 participants from 6 cohorts for CHD mortality, followed for 460,333 person-years, and 33,394 participants from 4 cohorts for CHD events.

### Data synthesis

Among 38,274 adults (median age 55 years, 63% women), 1691 (4.4%) had subclinical hypothyroidism, of whom 775 (45.8%) had positive TPOAb. During follow-up, 1436 participants died of CHD and 3285 had CHD events. Compared to euthyroid individuals, age- and gender-adjusted risks of CHD mortality in subclinical hypothyroidism were similar among individuals with and without TPOAb (HR=1.15, 95%CI 0.87 to 1.53, vs. HR=1.26, CI 1.01 to 1.58, p for interaction 0.62), as were risks of CHD events (HR=1.16, CI 0.87 to 1.56 vs. HR=1.26, CI 1.02 to

1.56, p for interaction 0.65). 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 auto-immunity do not add independent prognostic information for CHD outcomes.

## Introduction

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 thyrotropin level [4.5-19.9 mIU/L] and normal free thyroxin [T4] level) was associated with coronary heart disease (CHD) mortality and CHD events, with stronger association for those with thyrotropin (also known as thyroid-stimulating hormone, TSH) ≥10.0 mIU/L (5).

The presence of thyroid antibodies predicts the risk of progression from subclinical to overt hypothyroidism (6-9). Among 1877 subjects (56% women), both raised TSH level and the presence of thyroid antibodies at baseline were associated with development of hypothyroidism over 20-year follow-up (6). Among 92 women (mean age 50.7 years) with subclinical hypothyroidism followed for 9 years, the incidence of overt hypothyroidism increased from 23.2% to 58.5% with the presence of anti-microsomal antibodies (p=0.03) (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 or not 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 had also limited power with a relatively low number of events and did not provide subgroup analyses (e.g. 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).

# 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 30 June 2011, with no language restriction, and screened bibliographies of selected articles (Appendix Methods). We included studies with *a priori* criteria: full-text published longitudinal cohort studies, reporting baseline levels of thyroid function (TSH and T4) and antibodies, with a control euthyroid group and prospective follow-up of cause-specific mortality and CHD outcomes. We excluded studies where only participants taking thyroid medications (anti-thyroid drugs, thyroxin, or amiodarone) or participants with only overt hypothyroidism (high TSH and low T4 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 T4 or total T4 in one study (14), thyroid antibodies, baseline cardiovascular risk factors (i.e. blood pressure, cigarette smoking status, total cholesterol level, diabetes mellitus), body mass index (weight in kilograms divided by squared height in meters [$kg/m^2$]), 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 T4 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 radioimmunoassay in this study that gives higher measured TSH values than current assays (23). For participants in the Study of Health in Pomerania (24), a 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 *hyper*thyroid (n=706, 18.4%) and very few subclinically *hypo*thyroid (n=13, 0.4%). For T4 level, we used study- and method-specific cutoff values (Appendix Table 1), as this measurement shows greater inter-method variation than TSH assays. Eight participants among 1691 with TSH 4.5-19.9 mIU/L had missing T4 values (Appendix Table 1): 7 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 T4 values.

Thyroid antibodies were measured by different assays in the original cohorts and we used assay-specific cutoff values (Appendix Table 1). In two older cohorts, levels of anti-microsomal antibodies (22) and thyroid anticytoplasmic antibodies (14) were available instead of the more precise thyroid peroxidase antibodies (TPOAb) 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, then at baseline and during follow-up, as well as analyses limited to participants with TSH ≥10.0 mIU/L.

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 (Appendix Table 1). We defined CHD events as non-fatal myocardial infarction 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 interview, review of medical records, and other support documents without 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 9.2, SAS Institute Inc, Cary, NC; Stata 12.1, StataCorp, College Station, TX). 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 5.1.7, Nordic Cochrane Centre, Copenhagen, Denmark). 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 TPOAb to predict CHD outcomes in subclinical hypothyroidism by interaction tests: we compared pooled estimates of 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)), then further adjusted for cardiovascular risk factors (systolic blood pressure, smoking status, total cholesterol, diabetes), body mass index, lipid-lowering and antihypertensive medications. To explore potential sources of heterogeneity, we performed pre-defined 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 6 prospective cohorts meeting all inclusion criteria (Appendix Figure 1) comprising 38,274 adults (median age 55 years, 62.9% women) recruited from the general population. 36,583 were euthyroid and 1691 (4.4%) had subclinical hypothyroidism, of whom 775 (45.8%) had positive TPOAb (Table 1). Median follow-up was 12.2 years (interquartile range 11.2-13.1 years) for a total of 460,333 person-years, with a loss to follow-up rate <5% in all included studies.

During follow-up, 1436 participants died of CHD in the whole sample, and 3285 CHD events occurred among 33,394 participants from 4 cohorts having data on CHD events (14-16, 22) (Table 2). In age and sex-adjusted analyses compared to euthyroid individuals, risks of CHD mortality were similar among those with TPOAb-positive subclinical hypothyroidism (HR 1.15, CI 0.87 to 1.53) and those with TPOAb-negative subclinical hypothyroidism (HR 1.26, CI 1.01 to 1.58, p for interaction 0.62) (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 to 1.56 vs. HR 1.26, CI 1.02 to 1.56, respectively, p for interaction 0.65) (Appendix Figure 2). As 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 to our previous analyses with 11 cohorts (5). However, at each TSH level, risks did not differ by TPOAb status (Figure 1). Risks differed slightly according to sex and age, though the interaction terms were not statistically significant (p for interaction ≥0.39 for sex and >0.05 for age categories, Table 2).

Sensitivity analyses yielded comparable results (Table 3). The exclusion of thyroid medication users at baseline or during follow-up yielded similar results including after further excluding 2

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 body mass index. Limiting analyses to studies with recent thyroid antibodies assays or to participants with TSH ≥10.0 mIU/L yielded overall higher risks of CHD mortality and events but estimates did not differ according to TPOAb status (Appendix Table 2).

When analyzing data from the four cohorts that measured TPOAb in all participants irrespective of TSH (n=9151) (14, 15, 24, 35), the overall prevalence of TPOAb positivity was 6.5% (Appendix Table 3). In age and sex-adjusted analyses, CHD mortality risk was similar in the population with positive TPOAb compared to those with negative TPOAb (HR 1.09, CI 0.75 to 1.58), as well as for CHD events (HR 1.19, CI 0.93 to 1.53). Stratified analyses by gender yielded similar results (both p for interaction ≥0.40). 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 euthyroid state and 116 (25.3%) with subclinical hypothyroidism developed HF. 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 to 1.14) and those with thyroid antibody-negative subclinical hypothyroidism (HR 1.01, CI 0.79 to 1.28, p for interaction 0.37). Power was insufficient to assess HF risks stratified both by thyroid antibodies and TSH levels or other subgroups.

The proportional hazard assumption was consistent across studies (all p>0.10). 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=0.50) and CHD events (p=0.060).

## Discussion

In this analysis of data from more than 38,000 individuals recruited in 6 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.* found no association between the presence of TPOAb in subclinical hypothyroidism and subsequent myocardial infarction events among post-menopausal women (17). Similar results were also found for reports of single cohorts included in the Thyroid Studies Collaboration, such as the Whickham Survey (14), the HUNT Study (Nord-Trøndelag Health Study) (16), and the Busselton Health Study (15). However, in the Rotterdam Study, the presence of positive TPOAb in subclinical hypothyroidism was associated with prevalent myocardial infarction compared to euthyroid women (18), but there were not enough events for prospective analysis of this association (16 first incident myocardial infarctions over 4.6 years) (21).

Because thyroid auto-immunity 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 levothyroxin treatment, as recommended by some current guidelines (3), and that such treatment may have reduced the risk of CHD. However, our sensitivity analysis 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 and levels of TSH (5), without an independent contribution from autoimmune dysfunction. This adds to current knowledge about the pathophysiology of thyroid-related CHD.

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 13-year change in TSH, FT4 levels, and TPOAb positivity and mortality (39). Third, older thyroid antibodies assays were used in two included cohorts (anti-microsomal antibodies (22) and thyroid cytoplasmic antibodies (14)), but sensitivity analyses excluding cohorts with older assays yielded similar results. Because thyroglobulin antibodies (TgAb) were not available in the three

largest cohorts, there was insufficient power to examine the risks associated with thyroglobulin antibodies. However, the lack of TgAb in our analyses should not be a major limitation, because most people (70%) who had positive TgAb in NHANES III also had positive TPOAb (2). Moreover, both in NHANES III (cross-sectional (2)) and the Busselton Health Study (longitudinal analysis (40)), 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 out 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 thyroxine. However, sensitivity analyses excluding thyroid medication users yielded similar results.

Current guidelines for the management of subclinical hypothyroidism are conflicting about measuring TPOAb to target treatment in patients with subclinical hypothyroidism (1, 3). Although the presence of TPOAb 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 auto-immunity 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).

## Acknowledgements

### Participating Studies of the Thyroid Studies Collaboration

*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. *Brazil*: Brazilian Thyroid Study.

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## Role of the Sponsor

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.

## Ethical approval

Each of the original cohort studies has been approved by its respective Institutional Review Board.

## Statistical Evaluation

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

## Author Contributions

Dr Collet and Dr Rodondi 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.

Study concept and design: Rodondi, Bauer, Gussekloo, Cappola

Acquisition of data: Gussekloo, Cappola, Åsvold, Sgarbi, Völzke, Walsh

Analysis and interpretation of data: Collet, Bauer, Cappola, Weiler, Vittinghoff, Gussekloo, Åsvold, Bremner, den Elzen, Maciel, Vanderpump, Dörr, Wallaschofski, Newman, Sgarbi, Razvi, Völzke, Walsh, Aujesky, Rodondi

Drafting of the manuscript: Collet, Rodondi

Critical revision of the manuscript for important intellectual content: Collet, Bauer, Cappola, Weiler, Vittinghoff, Gussekloo, Åsvold, Bremner, den Elzen, Maciel, Vanderpump, Dörr, Wallaschofski, Newman, Sgarbi, Razvi, Völzke, Walsh, Aujesky, Rodondi

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Study supervision: Rodondi, Bauer

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## Table 1

Baseline characteristics of individuals with euthyroidism or subclinical hypothyroidism with measured thyroid antibodies

| Study | Description of study sample | No | Median age (range) * | Women, no (%) | Subclinical hypothyroidism, no (%) † | Subclinical hypothyroidism with positive TPOAb, no (%) ‡ | Thyroid medication at baseline / during follow-up, no (%) § | Follow-up ‖ | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Start | Median duration (IQR) / Person-years |
| *United States* | | | | | | | | | |
| Cardiovascular Health Study (22) | Community-dwelling adults with Medicare eligibility in 4 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 |

## Table 1 (footnotes)

Abbreviations: IQR, interquartile range ($25^{th}$-$75^{th}$ percentiles); NA, data not available; TPOAb, thyroid peroxidase antibodies.

* Participants younger than 18 years were excluded.

† The Whickham Survey used a 1st generation TSH assay, which gives higher values than current assays, thus a TSH range of 6.0 to 21.5 mIU/L was used for subclinical hypothyroidism (14). Participants in SHIP had iodine supplementation a few years before inclusion, thus a TSH reference range (0.25-2.12 mIU/L) was used as suggested (25).

‡ No. 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).

§ Data on thyroid medication use (thyroxine, 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 (Nord-Trøndelag Health Study) (16) and the Brazilian Thyroid Study (35) during follow-up.

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

## Table 2

Age- and sex-adjusted analyses for the association of subclinical hypothyroidism (SH) with coronary heart disease (CHD) mortality and CHD events, according to measured thyroid antibody status

| | CHD Mortality * | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Euthyroidism | | SH with negative TPOAb status | | SH with positive TPOAb status | | SH with negative TPOAb vs. euthyroidism | SH with positive TPOAb vs. euthyroidism | |
| | Events | Participants | Events | Participants | Events | Participants | HR (95% CI) | HR (95% CI) | *P for interaction* |
| *Total population* | 1301 | 36,583 | 85 | 916 | 50 | 775 | 1.26 (1.01, 1.58) | 1.15 (0.87, 1.53) | *0.62* |
| *Sex* | | | | | | | | | |
| Men | 720 | 13,720 | 38 | 322 | 19 | 152 | 1.16 (0.84, 1.62) | 1.38 (0.80, 2.37) | *0.59* |
| Women | 581 | 22,863 | 47 | 594 | 31 | 623 | 1.41 (1.04, 1.90) | 1.21 (0.84, 1.73) | *0.53* |
| *P for interaction* | | | | | | | *0.39* | *0.70* | |
| *Age* ‡ | | | | | | | | | |
| 18-49 years | 50 | 11,704 | 1 | 173 | 1 | 162 | 2.41 (0.55, 10.61) § | 4.88 (1.20, 19.96) § | *0.50* |
| 50-64 years | 210 | 11,210 | 10 | 221 | 4 | 196 | 2.71 (1.12, 6.53) § | 1.83 (0.72, 4.63) § | *0.55* |
| 65-79 years | 805 | 9630 | 64 | 432 | 34 | 344 | 1.49 (1.15, 1.93) | 1.04 (0.74, 1.47) | *0.10* |
| ≥ 80 years | 212 | 1381 | 10 | 88 | 11 | 41 | 0.60 (0.32, 1.13) § | 1.71 (0.92, 3.19) § | *0.02* |
| *P for trend* | | | | | | | *0.057* | *0.12* | |
| *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) | *0.39* |
| 7.0-9.9 mIU/L | | | 11 | 133 | 13 | 173 | 1.09 (0.47, 2.54) § | 1.28 (0.75, 2.18) § | *0.75* |
| 10.0-19.9 mIU/L | | | 5 | 50 | 14 | 120 | 1.64 (0.75, 3.56) § | 1.70 (1.01, 2.86) § | *0.94* |
| *P for trend* | | | | | | | *0.33* | *0.047* | |

## Table 2 (*cont.*)

Age- and sex-adjusted analyses for the association of subclinical hypothyroidism (SH) with coronary heart disease (CHD) mortality and CHD events, according to measured thyroid antibody status

| | CHD Events [†] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Euthyroidism | | SH with negative TPOAb status | | SH with positive TPOAb status | | SH with negative TPOAb vs. euthyroidism | SH with positive TPOAb vs. euthyroidism | |
| | Events | Participants | Events | Participants | Events | Participants | HR (95% CI) | HR (95% CI) | *P for interaction* |
| *Total population* | 2995 | 31,903 | 174 | 774 | 116 | 717 | 1.26 (1.02, 1.56) | 1.16 (0.87, 1.56) | *0.65* |
| *Sex* | | | | | | | | | |
| Men | 1609 | 11,392 | 79 | 273 | 36 | 133 | 1.16 (0.92, 1.46) | 0.99 (0.66, 1.48) | *0.51* |
| Women | 1386 | 20,511 | 95 | 501 | 80 | 584 | 1.27 (1.02, 1.59) | 1.18 (0.94, 1.48) | *0.65* |
| *P for interaction* | | | | | | | 0.58 | 0.46 | |
| *Age* [‡] | | | | | | | | | |
| 18-49 years | 322 | 11,697 | 6 | 122 | 7 | 161 | 1.44 (0.66, 3.14) | 2.13 (1.00, 4.55) | *0.48* |
| 50-64 years | 660 | 10,160 | 21 | 164 | 10 | 185 | 1.72 (1.10, 2.69) [§] | 0.98 (0.38, 2.54) [§] | *0.29* |
| 65-79 years | 1686 | 8627 | 123 | 400 | 84 | 330 | 1.20 (1.00, 1.45) | 1.11 (0.79, 1.56) | *0.69* |
| ≥ 80 years | 306 | 1380 | 24 | 88 | 15 | 41 | 1.04 (0.68, 1.57) [§] | 1.54 (0.63, 3.75) [§] | *0.44* |
| *P for trend* | | | | | | | 0.33 | 0.65 | |
| *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) | *0.50* |
| 7.0-9.9 mIU/L | | | 28 | 118 | 28 | 165 | 1.22 (0.75, 2.00) | 1.07 (0.74, 1.56) | *0.67* |
| 10.0-19.9 mIU/L | | | 16 | 41 | 24 | 115 | 2.60 (1.43, 4.74) | 1.23 (0.61, 2.47) | *0.11* |
| *P for trend* | | | | | | | *0.002* | *0.57* | |

## Table 2 (footnotes)

Abbreviations: CI, confidence interval; CHD, coronary heart disease; HR, hazard ratio (all age- and sex-adjusted); NA, data not applicable; SH, subclinical hypothyroidism; TPOAb, thyroid peroxidase antibodies.

* 21 participants were excluded from the analyses of CHD mortality because of missing cause of death.

† 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.

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

§ Strata from specific studies were excluded when there were <5 events or an empty comparison group.

## Table 3

Sensitivity analyses for the association of subclinical hypothyroidism (SH) with coronary heart disease (CHD) mortality and CHD events, according to measured thyroid antibody status

| | CHD Mortality | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Euthyroidism | | SH with negative TPOAb status | | SH with positive TPOAb status | | SH with negative TPOAb vs. euthyroidism | SH with positive TPOAb vs. euthyroidism | *P for interaction* |
| | Events | Participants | Events | Participants | Events | Participants | HR (95% CI) | HR (95% CI) | |
| ***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) | *0.62* |
| Fixed-effects model | 1301 | 36,583 | 85 | 916 | 50 | 775 | 1.26 (1.01, 1.58) | 1.15 (0.87, 1.53) | *0.62* |
| ***Excluding participants*** | | | | | | | | | |
| Excluding those with missing T4 * | 1301 | 36,583 | 84 | 912 | 49 | 771 | 1.26 (1.00, 1.57) | 1.13 (0.85, 1.51) | *0.56* |
| Excluding thyroid medication users at baseline † | 1279 | 36,289 | 83 | 899 | 49 | 766 | 1.26 (1.01, 1.58) | 1.13 (0.85, 1.51) | *0.53* |
| Excluding thyroid medication users at baseline or during follow-up † | 1269 | 36,076 | 78 | 834 | 44 | 682 | 1.34 (1.07, 1.69) | 1.28 (0.94, 1.72) | *0.79* |
| ***Excluding studies*** | | | | | | | | | |
| Excluding studies with older thyroid antibody assays ‡ | 711 | 31,775 | 32 | 562 | 17 | 547 | 1.56 (1.09, 2.23) | 1.21 (0.75, 1.94) | *0.41* |
| 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) | *0.62* |
| 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) | *0.47* |
| ***Further adjustments in multivariate (MV) models*** § | | | | | | | | | |
| 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) | *0.62* |
| 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) | *0.72* |
| MV model 1 + body mass index | 1276 | 36,234 | 82 | 908 | 48 | 776 | 1.25 (1.00, 1.57) | 1.13 (0.84, 1.50) | *0.59* |

## Table 3 (*cont.*)

Sensitivity analyses for the association of subclinical hypothyroidism (SH) with coronary heart disease (CHD) mortality and CHD events, according to measured thyroid antibody status

| | CHD Events | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 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 | | | |
| ***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) | *0.65* |
| Fixed-effects model | 2995 | 31,903 | 174 | 774 | 116 | 717 | 1.20 (1.03, 1.41) | 1.08 (0.90, 1.31) | *0.39* |
| ***Excluding participants*** | | | | | | | | | |
| Excluding those with missing T4 * | 2995 | 31,903 | 172 | 770 | 115 | 713 | 1.26 (1.01, 1.56) | 1.17 (0.86, 1.59) | *0.70* |
| Excluding thyroid medication users at baseline † | 2967 | 31,805 | 172 | 768 | 115 | 711 | 1.24 (1.02, 1.51) | 1.15 (0.87, 1.54) | *0.67* |
| Excluding thyroid medication users at baseline or during follow-up † | 2934 | 31,695 | 155 | 715 | 93 | 638 | 1.25 (1.06, 1.47) | 1.12 (0.88, 1.41) | *0.46* |
| ***Excluding studies*** | | | | | | | | | |
| Excluding studies with older thyroid antibody assays ‡ | 1599 | 27,138 | 54 | 422 | 40 | 489 | 1.49 (1.13, 1.95) | 1.28 (0.74, 2.22) | *0.63* |
| 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) | *0.53* |
| ***Further adjustments in multivariate (MV) models*** § | | | | | | | | | |
| 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) | *0.65* |
| 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) | *0.78* |
| MV model 1 + body mass index | 2940 | 31,587 | 169 | 766 | 114 | 709 | 1.23 (1.01, 1.50) | 1.17 (0.87, 1.58) | *0.78* |

## Table 3 (footnotes)

Abbreviations: CI, confidence interval; CHD, coronary heart disease; HR, hazard ratio (all age and sex-adjusted, unless stated otherwise); MV, multivariate; NA, not applicable; SH, subclinical hypothyroidism.

* 8 participants were excluded in this analysis: Cardiovascular Health Study 6, Whickham Survey 1 and Busselton Health Study 1.

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

‡ Studies with older thyroid auto-antibodies assays were excluded: anti-microsomal antibodies in the Cardiovascular Health Study (22) and thyroid cytoplasmic antibodies in the Whickham Survey (14).

§ Some participants were excluded from MV models because of lack of data on covariates.

## Figure 1

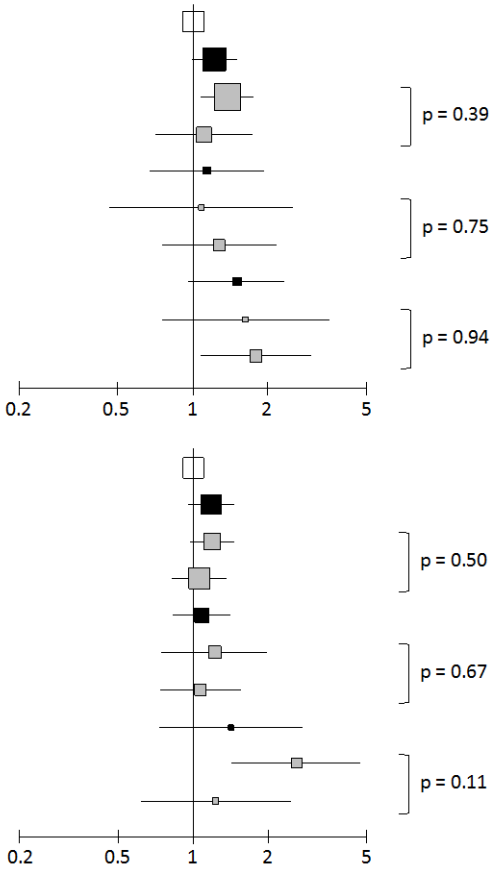
Hazard ratios of coronary heart disease (CHD) mortality and events for subclinical hypothyroidism vs. euthyroidism, according to thyrotropin (thyroid-stimulating hormone, TSH) level and thyroid peroxidase antibodies (TPOAb) status

Legend: 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.

Original file: *Figure 1.ppt*, below as image for peer-reviewers' convenience.

**Figure 1. Hazard ratios of coronary heart disease (CHD) mortality and events for subclinical hypothyroidism vs. euthyroidism, according to thyrotropin (thyroid-stimulating hormone, TSH) level and thyroid peroxidase antibodies (TPOAb) status**

| TSH level and TPOAb | No. of events | No. of participants | Hazard Ratios and 95% Confidence Intervals | Interaction test |
|---|---|---|---|---|
| **CHD mortality** [a] | | | | |
| **0.45-4.49 mIU/L** | **1301** | **36,583** | **1 (reference)** | |
| **4.5-6.9 mIU/L** | **92** | **1208** | **1.23 (1.00, 1.53)** | |
| *negative TPOAb* | 69 | 733 | 1.39 (1.09, 1.78) | p = 0.39 |
| *positive TPOAb* | 23 | 475 | 1.11 (0.71, 1.74) | |
| **7.0-9.9 mIU/L** | **24** | **311** | **1.15 (0.67, 1.96)** | |
| *negative TPOAb* | 11 | 133 | 1.09 (0.47, 2.54) | p = 0.75 |
| *positive TPOAb* | 13 | 178 | 1.28 (0.75, 2.18) | |
| **10.0-19.9 mIU/L** | **19** | **172** | **1.52 (0.97, 2.38)** | |
| *negative TPOAb* | 5 | 50 | 1.64 (0.75, 3.56) | p = 0.94 |
| *positive TPOAb* | 14 | 122 | 1.80 (1.07, 3.01) | |
| **CHD events** [b] | | | | |
| **0.45-4.49 mIU/L** | **2995** | **31,903** | **1 (reference)** | |
| **4.5-6.9 mIU/L** | **194** | **1052** | **1.18 (0.95, 1.46)** | |
| *negative TPOAb* | 130 | 615 | 1.19 (0.96, 1.46) | p = 0.50 |
| *positive TPOAb* | 64 | 437 | 1.06 (0.82, 1.37) | |
| **7.0-9.9 mIU/L** | **56** | **283** | **1.08 (0.83, 1.41)** | |
| *negative TPOAb* | 28 | 118 | 1.22 (0.75, 2.00) | p = 0.67 |
| *positive TPOAb* | 28 | 165 | 1.07 (0.74, 1.56) | |
| **10.0-19.9 mIU/L** | **40** | **156** | **1.42 (0.73, 2.75)** | |
| *negative TPOAb* | 16 | 41 | 2.60 (1.43, 4.74) | p = 0.11 |
| *positive TPOAb* | 24 | 115 | 1.23 (0.61, 2.47) | |




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.