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# Role of subclinical thyroid dysfunction on the occurrence of cardiovascular events and mortality

**Baris Gencer[1], MD; Tinh-Hai Collet[2], MD; Vanessa Virgini[3], MD; Reto Auer[4], MD; Nicolas Rodondi[3] MD, MAS**

Authors' affiliations:

[1] Cardiology Division, Department of Medicine, Geneva University Hospital, Switzerland
[2] Endocrinology Division, Department of Medicine, Lausanne University Hospital
[3] Department of General Internal Medicine, University of Bern, Switzerland
[4] Department of Epidemiology and Biostatistics, University of California, San Francisco

**Corresponding author**

Prof. Dr. Nicolas Rodondi, MD, MAS
Head of Ambulatory Care
Department of General Internal Medicine,
Inselspital, University of Bern, Switzerland
Phone: + 41 31 632 41 63
Fax: + 41 31 632 88 85
Email : Nicolas.Rodondi@insel.ch

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## Abstract

The association between subclinical thyroid dysfunction and cardiovascular outcomes has been recently clarified with the publication of three individual participant data (IPD) analyses from the Thyroid Studies Collaboration. We identified original cohort studies in a systematic review and pooled individual data from over 55'000 participants to get a more precise estimate of the risks of cardiovascular outcomes associated with subclinical thyroid dysfunction.

Subclinical hypothyroidism and subclinical hyperthyroidism, defined as normal thyroxine levels with increased or decreased thyrotropin (TSH) respectively, are associated with increased risk of cardiovascular outcomes compared to euthyroid state, particularly in those with a more pronounced thyroid dysfunction. Specifically, subclinical hypothyroidism is associated with an increased risk of coronary heart disease (CHD) events, CHD mortality and heart failure events in individuals with higher TSH levels, particularly in those with TSH levels ≥10.0 mIU/L. Conversely, subclinical hyperthyroidism is associated with an increased risk of total mortality, CHD mortality, heart failure and atrial fibrillation, particularly in those with suppressed TSH levels <0.10 mIU/L.

Pending future randomized controlled trials, these observational findings allow identifying potential TSH thresholds for thyroid medication initiation based on clinical outcomes, although clinical decision based solely on observational data need caution. The impact of thyroid replacement among the elderly with subclinical hypothyroidism will be studied in a multicenter international randomized controlled trial (Thyroid Hormone Replacement for Subclinical Hypothyroidism Trial, TRUST trial).

## Introduction

In contrast to overt dysfunction, the evidence for treating subclinical thyroid dysfunction is still subject to controversy.(1-3) (+ ref Gharib) Current guidelines are based on expert consensus, sometimes with diverging conclusions,(ref Gharib) and the debate persists whether screening of subclinical thyroid dysfunction should be conducted. The treatment of subclinical thyroid dysfunction aims to prevent progression to overt dysfunction and cardiovascular complications, but it may also prevent osteoporosis and improve mood, muscular and cognitive function.(4)

The prevalence of subclinical thyroid disorder increases with age (ref NHANES Hollowell), as well as heart failure (HF) especially among the elderly.(5) HF remains one of the most frequent cause of hospitalizations in persons older than 65 years (ref?). Data on the association between subclinical thyroid dysfunction and the risk of coronary heart disease (CHD), HF and atrial fibrillation (AF) is conflicting among several large prospective cohorts and meta-analyses.(6-8) Furthermore, interpretation of those studies was hampered by several methodological issues. (9)

The publication of three recent pooled individual participant data (IPD) analyses has permitted to strengthen the association between subclinical thyroid dysfunction and cardiovascular outcomes.(order refs by pub date)(10-12) Subclinical thyroid dysfunction is an easy to treat condition that might have a role in the prevention of the occurrence of cardiovascular outcomes. However, no randomized controlled trials has reported on the potential benefits and harms of the treatment of subclinical thyroid dysfunction.

In this review, we will describe the association between subclinical hypothyroidism and cardiovascular outcomes such as CHD, HF and cardiovascular mortality, and similarly the association between subclinical hyperthyroidism and CHD, HF, incident AF and mortality. As pathophysiological mechanisms behind subclinical thyroid dysfunction on the cardiovascular

system have been extensively described, these will not be the main subject of this review. (13-17) (I would keep only Biondi 2008: it is the most thorough review: 60 pages!)

## The Thyroid Studies Collaboration

The recent IPD publications were performed within a research network of experts entitled "The Thyroid Studies Collaboration".(3 ref) After a systematic review,(6) all available published cohorts that assessed prospectively the relation between subclinical thyroid dysfunction and cardiovascular outcomes were invited to join the Collaboration and share individual data. Data from different cohorts were pooled and summarized as recommended using forest plots (Ref [18,19]) This process has been repeated for each different cardiovascular disease (CVD) outcomes.

IPD analysis is indeed the best known method to assess the impact of different subgroups on the occurrence of different clinical outcomes using standard definition of predictors and outcomes. (18, 19)(keep Simmonds 2005) Pooling different dataset across several cohorts increases power to detect epidemiological associations that might be undetectable in one cohort or conflicting results between cohorts. IPD analysis is considered the optimal design to summarize evidence across studies. It permits to reduce potential bias from study level meta-analyses (ecological fallacy), to adjust with same confounders and to perform time-to-event analyses.(19-21) Data from different cohorts were pooled and summarized as recommended using forest plots for each outcome. (22, 23)

The Thyroid Studies Collaboration is open to collaborate with authors of other published cohorts in the future. Such a large and international collaboration is an opportunity to perform research on the association between subclinical thyroid disorder and cardiovascular diseases.

# Subclinical Hypothyroidism

## Definition and Epidemiology

Subclinical hypothyroidism is defined as a Thyroid-Stimulating Hormone (TSH, or thyrotropin) level above the upper limit of the reference range with normal free thyroxine (FT4) concentration. Guidelines recommend to reassess serum TSH level within 3 to 6 months to confirm persistent TSH abnormalities. (ref 4) For the IPD analyses, we used a uniform TSH cutoff level (>4.5 mIU/L), based on an expert consensus meeting of our Thyroid Studies Collaboration (International Thyroid Conference, Paris, 2010), expert reviews (ref Surks, Helfand) and previous large cohorts (ref Cappola, Walsh, Boekholdt).

Subclinical thyroid dysfunction is more common than overt dysfunction, with a prevalence for subclinical hypothyroidism reaching up to 10% among the elderly.(15) Subclinical hypothyroidism is a transitory laboratory finding in a fair amount of cases, partially due to laboratory imprecision, especially when TSH levels are ≤10.0 mIU/L. Up to 60% of persons with subclinical hypothyroidism will spontaneously revert to a euthyroid state, while 1-5% per year will progress to an overt thyroid dysfunction.(check ref Somwaru, JCEM,2012) The presence of antithyroid antibodies, such as anti-thyroid peroxidase antibodies (TPOAb), has been associated with an increased risk of progression to overt thyroid dysfunction,(ref Somwaru) but their use in clinical decisions is still subject to controversy.(24)

## Subclinical hypothyroidism and cardiovascular system

Subclinical hypothyroidism has been associated with cardiac abnormalities, such as left ventricular dysfunction and depressed systolic function at rest and during effort. This condition has also been associated with vascular abnormalities, such as increased vascular resistance, arterial stiffness, changes in endothelial function, and atherosclerosis.(25) Higher TSH levels have been correlated with decreased left ventricular stroke volume, decreased in cardiac index, and increased systemic vascular resistance.(26) Restoration of a euthyroid state

in patients with subclinical hypothyroidism was found to normalize different cardiac and vascular structural parameters.(14, 27-29)

**Subclinical hypothyroidism and total and CHD mortality**

The IPD analysis (ref Rodondi, JAMA, 2010) for the association between subclinical hypothyroidism and total mortality pooled 51'837 euthyroid and 3450 participants with subclinical hypothyroidism from 11 prospective cohorts in the Unites States, Australia, Asia, South America and Europe (**Table 1**). (30-40) Compared to euthyroidism, the age and gender-adjusted hazard ratio (HR) for total mortality with subclinical hypothyroidism was 1.09 (95% confidence interval [CI], 0.96-1.24). In contrast to CHD events and mortality, the risk of total mortality was not significantly increased with higher TSH levels. (**Figure 1**)

The IPD analysis (11) for the association between subclinical hypothyroidism and CHD mortality pooled 10 studies with 50'953 euthyroid and 3348 participants with subclinical hypothyroidism (**Table 1**). (30-33, 35-39, 41) Compared to euthyroidism, the age and gender-adjusted HR for CHD mortality with subclinical hypothyroidism was 1.14 (95% CI, 0.99-1.32) and increased significantly with higher levels of TSH (p for trend 0.005), particularly in those with a TSH between 7.0-9.9 mIU/L (HR 1.42, 95% CI 1.03-1.95) and a TSH ≥10.0 mIU/L (HR 1.58, 95% CI 1.10-2.27) (**Figure 2**).

**Subclinical hypothyroidism and CHD events**

The IPD analysis (11) for the association between subclinical hypothyroidism and CHD events included 23'957 euthyroid participants and 2020 with subclinical hypothyroidism from 7 prospective studies in United Stated, Australia and Europe (**Table 2**). (30, 31, 33, 35-38) Compared to euthyroidism, the age and gender-adjusted HR for CHD events with subclinical hypothyroidism was 1.18 (95% CI 0.99-1.42). The risk of CHD events increased significantly with higher levels of TSH (p for trend <0.001), particularly in those with TSH levels ≥10.0 mIU/L (HR 1.89, 95% CI 1.28-2.80) (**Figure 3**). Minimal TSH disturbances were not

associated with CHD events: HR was 1.00 (95% CI 0.86-1.18) for a TSH between 4.5 and 6.9 mIU/L.

**Subclinical hypothyroidism and HF events**

The IPD analysis of 25'390 participants from 6 prospective cohorts in the Unites States and Europe (30, 31, 33, 35, 42, 43) showed that the risk of HF events was increased with higher levels of TSH, particularly in those with TSH ≥10.0 mIU/L (**Table 2**). (12) Considering the total population of participants with subclinical thyroid dysfunction (TSH 4.5-19.9 mIU/L), the risk was not significantly increased, because the majority of participants had a mild TSH disturbance (TSH 4.5-6.9 mIU/L) (**Figure 4**). These results confirmed that subclinical thyroid dysfunction is a heterogeneous identity with varying risk of HF events according to TSH levels as observed with CHD events and CHD mortality. As previously described, ventricular diastolic dysfunction has been associated with subclinical hypothyroidism and might precede the clinical development of HF observed across prospective cohorts. (44) In addition to the cardiac structure abnormalities associated with higher TSH levels, the increased risk of CHD events might also contribute to the development of HF, as CHD is a common cause of HF. (45, 46) However, the exclusion of preexisting CVD in sensitivity analyses did not change the findings. (12)

## Subclinical Hyperthyroidism

**Definition and Epidemiology**

Subclinical hyperthyroidism is defined as a serum TSH concentration below the lower limit of the reference range (<0.45 mIU/L) with normal serum FT4 and free tri-iodothyronine (FT3). (1, 2, 24) For the IPD analyses, we again used a uniform TSH cutoff level (<0.45 mIU/L), based on an expert consensus meeting of our Thyroid Studies Collaboration (International Thyroid Conference, Paris, 2010), expert reviews (ref Surks, Helfand) and previous large

cohorts (ref Cappola, Walsh, Boekholdt). In order to study the risks associated with endogenous subclinical hyperthyroidism and the iatrogenic counterpart, we excluded participants on thyroid medication at baseline.

The prevalence of subclinical hyperthyroidism is approximately 1%, but varies according to age, gender and iodine intake. (15) Subclinical hyperthyroidism might be a transitory abnormality that occurs when TSH levels are low with normal FT3 and FT4. In fact, up to 50% of persons with subclinical hyperthyroidism will spontaneously revert to a euthyroid state within several months, whereas 1-15% per year will progress to an overt dysfunction. (4)

**Subclinical hyperthyroidism and cardiovascular system**

FT3 has an important role in the regulation of cardiovascular system. High levels of FT3 are correlated with higher cardiac rate, increased frequency of atrial and ventricular premature beats, increased left ventricular mass and some systolic and diastolic abnormalities. (47) Thus abnormalities in addition to vascular changes, such as increased carotid intima-media thickness or carotid artery plaque might lead to an increased risk of mortality and cardiovascular disorders associated with subclinical hyperthyroidism.(8, 15, 47-49)

**Subclinical hyperthyroidism and total and CHD mortality**

The IPD analysis (ref) for the association between subclinical hyperthyroidism and total mortality combined 50'486 euthyroid and 2188 participants with subclinical hyperthyroidism from 10 prospective cohorts in the Unites States, Australia, South America and Europe (**Table 1**). Compared to euthyroidism, the age and gender-adjusted HR for total mortality with subclinical hyperthyroidism was 1.24 (95 % CI 1.06-1.46) (**Figure 1**). In contrast to CHD mortality, the risk of total mortality was not significantly increased with lower TSH levels, possibly due to the low number of events in this category.

The IPD analysis (ref) for the association between subclinical hyperthyroidism and CHD mortality pooled 50'456 euthyroid and 2177 participants with subclinical hypothyroidism

from the same 10 cohorts (**Table 2**). Compared to euthyroidism, the age and gender-adjusted HR for CHD mortality with subclinical hyperthyroidism was 1.29 (95% CI 1.02-1.62). The risk increased significantly with lower levels of TSH (p for trend 0.02), particularly in those with a TSH <0.10 mIU/L (HR 1.84, 95% CI 1.12-3.00) (**Figure 2**).

**Subclinical hyperthyroidism and CHD events and incident AF**

The IPD analysis (ref) for the association between subclinical hyperthyroidism and CHD events included 21'714 euthyroid and 723 participants with subclinical hyperthyroidism from 6 prospective cohorts in the United States, Australia and Europe (**Table 2**). Compared to euthyroidism, the age and gender-adjusted HR for CHD events with subclinical hyperthyroidism was 1.21 (95% CI 0.99-1.46). The risk of CHD events was not significantly increased with lower TSH levels (**Figure 3**).

The risk of incident AF was also increased with subclinical hyperthyroidism: HR was 1.63 (95% CI 1.10-2.41) for TSH 0.10-0.44 mIU/L and 2.54 (95% CI 1.08-5.99) for TSH < 0.10 mIU/L (p for trend 0.02). The increased risk of AF events with subclinical hyperthyroidism were also reported in previous longitudinal studies.(30, 50-52)

**Subclinical hyperthyroidism and HF events**

The IPD analysis (ref) of 23'322 participants from 6 prospective cohorts in the United States and Europe (16, 18, 20, 28, 29) showed that the risk of HF increased with lower TSH levels, particularly in those with TSH levels <0.10 mIU/L (**Figure 4**). In fact, there was a significant parabolic association between TSH levels and the risk of HF events. The U-shaped curve of this association showed increased risks of HF for extreme TSH values, similarly to the risk of CHD mortality (**Figure 2**). Considering the total population with subclinical hyperthyroidism (<0.45 mIU/L), and as the majority of participants had slight disturbances of TSH levels (0.10-0.44 mIU/L), the risk of HF events was not significantly increased (HR 1.46, 95% CI

0.94-2.27) (**Table 2**). The observed association persisted after excluding preexisting HF or preexisting AF, which are common causes of HF hospitalization.

## Conclusion

Subclinical hypothyroidism is associated with an increased risk of CHD events, CHD mortality and HF events, but not of total mortality. The risk is increased with higher concentrations of TSH, particularly in those with TSH ≥10.0 mIU/L. Conversely, mild TSH elevations are not significantly associated with increased risks of cardiovascular outcomes. Endogenous subclinical hyperthyroidism is associated with an increased risk of total mortality, CHD mortality, CHD, AF and HF events. The risks of CHD mortality, AF and HF events are more pronounced with lower TSH levels, particularly in those with suppressed TSH levels <0.10 mIU/L. However, mild decrease of TSH levels are not associated with an increased risk of CHD events and total mortality. The risks were similar after further adjustment for cardiovascular risks factors. The stratified analyses according to gender, age and race did not significantly change the findings. Sensitivity analyses excluding those with thyroid medication or previous CVD did not alter results.

The three reported IPD analyses confirmed that subclinical thyroid dysfunction is a heterogeneous entity with varying risk of CVD and mortality according to TSH levels. The risk of different CVD is more pronounced with in both severe subclinical hypothyroidism and hyperthyroidism. In fact, these findings are compatible with a continuum between subclinical and overt thyroid dysfunction according to TSH levels. (16, 17) Individuals with mild TSH disturbances (4.5-6.9 mIU/L) are not at increased risk of cardiovascular outcomes based on the reviewed observational data, although a large proportion of this population is treated in clinical practice.(11, 53)

## Clinical implications

The findings from three IPD analyses have led to a better interpretation of TSH levels in the prevention and investigation of CHD, AF and HF events. While awaiting results from RCTs, these results may prove useful to define a TSH threshold for thyroid medication initiation based on clinical outcomes.,(54) However, as observational studies are subject to several limitations, clinical decision based only on these observational data should be made with great caution. The American College of Cardiology and the American Heart Association Guidelines for the diagnosis and management of HF in adults recommend the assessment of thyroid function to investigate conditions that might exacerbate HF, such as hypothyroidism or hyperthyroidism.(55) Studies on the addition of anti-thyroid antibodies in the prediction of cardiovascular events might be helpful to inform clinical decision making for patients with subclinical hypothyroidism. Recent guidelines recommend that "treatment of subclinical hyperthyroidism should be strongly considered in all individuals ≥65 years of age" with TSH level <0.10 mIU/L and "treatment of subclinical hyperthyroidism should be considered in individuals ≥ 65 years of age" with low TSH levels ≥0.10 mIU/L (ref Bahn). The recent findings in these IPD analyses are consistent with the current guidelines. In particular, the early recognition and treatment of subclinical hyperthyrodism might prevent the development of cardiac related complications, such as AF, HF and mortality.

Given the high prevalence of subclinical hypothyroidism and CVD among the elderly, a large randomized controlled trial has been started in Europe. The Thyroid Hormone Replacement for Subclinical Hypothyroidism trial (TRUST trial) will help to clarify the potential benefit of thyroxine replacement on the cardiovascular outcomes.

## Conflict of interest

None

## Acknowledgment

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## Abbreviations

ACC: American College of Cardiology

AF: Atrial Fibrillation

AHA: American Heart Association

CHD: Coronary Heart Disease

CI: Confidence intervals

CVD: Cardiovascular disease

FT4: Thyroxine

T3: Tri-iodothyronine

HF: Heart failure

HR: Hazard Ratio

IPD: Individual participant data

TSH: Thyroid stimulating Hormone

**Table 1 The risk of Total and CHD mortality according to subclinical thyroid dysfunction compared to euthyroidism**

| Study | Description of study sample | Total Mortality | | | CHD Mortality | | |
|---|---|---|---|---|---|---|---|
| | | Euthyroidism | Subclinical hypothyroidism | Subclinical hyperthyroidism | Euthyroidism | Subclinical hypothyroidism | Subclinical hyperthyroidism |
| *United States* | | | HR (95% CI) | HR (95% CI) | | HR (95% CI) | HR (95% CI) |
| Cardiovascular Health Study (30) | Community-dwelling adults with Medicare eligibility in 4 US communities | 1 (Ref) | 1.07 (0.95-1.21) | 1.04 (0.70-1.53) | 1 (Ref) | 1.09 (0.85-1.40) | 1.35 (0.67-2.72) |
| Health, Aging and Body Composition Study (31) | Community-dwelling adults with Medicare eligibility in 2 US communities | 1 (Ref) | 0.89 (0.72-1.11) | 1.25 (0.73-2.12) | 1 (Ref) | 0.85 (0.53-1.37) | 0.76 (0.19-3.09) |
| *Europe* | | | | | | | |
| Birmingham Study(32) | Community-dwelling adults aged ≥60 years from primary care practice in Birmingham, England | 1 (Ref) | 0.92 (0.64-1.33) | 1.39 (0.95-2.02) | 1 (Ref) | 1.21 (0.64-2.29) | 1.50 (0.73-3.09) |
| EPIC-Norfolk Study (33) | Adults living in Norfolk, England | 1 (Ref) | 0.97 (0.80-1.18) | 1.05 (0.82-1.36) | 1 (Ref) | 1.19 (0.83-1.72) | 1.24 (0.77-2.02) |
| HUNT Study (41) | Adults living in Nord-Trøndelag County, Norway | 1 (Ref) | 0.99 (0.82-1.19) | 1.52 (1.18-1.97) | 1 (Ref) | 1.09 (0.72-1.65) | 0.95 (0.42-2.13) |
| Leiden 85+ Study (35) | All adults aged 85 years living in Leiden, the Netherlands | 1 (Ref) | 0.85 (0.57-1.27) | 1.49 (0.95-2.32) | 1 (Ref) | 0.87 (0.27-2.82) | 0.65 (0.09-4.74) |
| Pisa cohort (36) | Patients admitted to cardiology department in Pisa, Italy [f] | 1 (Ref) | 2.13 (1.52-3.00) | 1.12 (0.71-1.74) | 1 (Ref) | 1.91 (1.08-3.36) | 1.93 (1.10-3.40) |
| Whickham Survey (37) | Adults living in and near Newcastle upon Tyne, England | 1 (Ref) | 0.98 (0.73-1.31) | NA | 1 (Ref) | 1.08 (0.64-1.81) | NA |
| SHIP (ref) | Adults living in Western Pomerania, Germany | 1 (Ref) | NA | 0.99 (0.81-1.21) | 1 (Ref) | NA | 1.08 (0.64-1.84) |
| PROSPER study (ref) | Older community-dwelling adults at high cardiovascular risk in the Netherland, Ireland. and Scotland | NA | NA | NA | NA | NA | NA |
| Bari cohort (ref) | Outpatients with HF followed up by Cardiology Department in Bari, Italy | NA | NA | NA | NA | NA | NA |
| *Australia* | | | | | | | |
| Busselton Health Study (ref) | Adults living in Busselton, Western Australia | 1 (Ref) | 1.44 (1.02-2.03) | 1.03 (0.57-1.88) | 1 (Ref) | 1.67 (0.94-2.97) | 0.91 (0.29-2.85) |
| *Southern America* | | | | | | | |
| Brazilian Thyroid Study (ref) | Adults of Japanese descent living in São Paulo, Brazil | 1 (Ref) | 1.96 (1.07-3.61) | 2.73 (1.53-4.88) | 1 (Ref) | | 2.35 (0.50-11.14) |
| *Asia* | | | | | | | |
| Nagasaki Adult Health Study (ref) | Atomic bomb survivors in Nagasaki, Japan | 1 (Ref) | 1.04 (0.83-1.31) | NA | 1 (Ref) | 0.67 (0.23-1.91) | NA |
| **Overall** | | **1 (Ref)** | **1.09 (0.96-1.24)** | **1.24 (1.06-1.46)** | **1 (Ref)** | **1.14 (0.99-1.32)** | **1.29 (1.02-1.62)** |

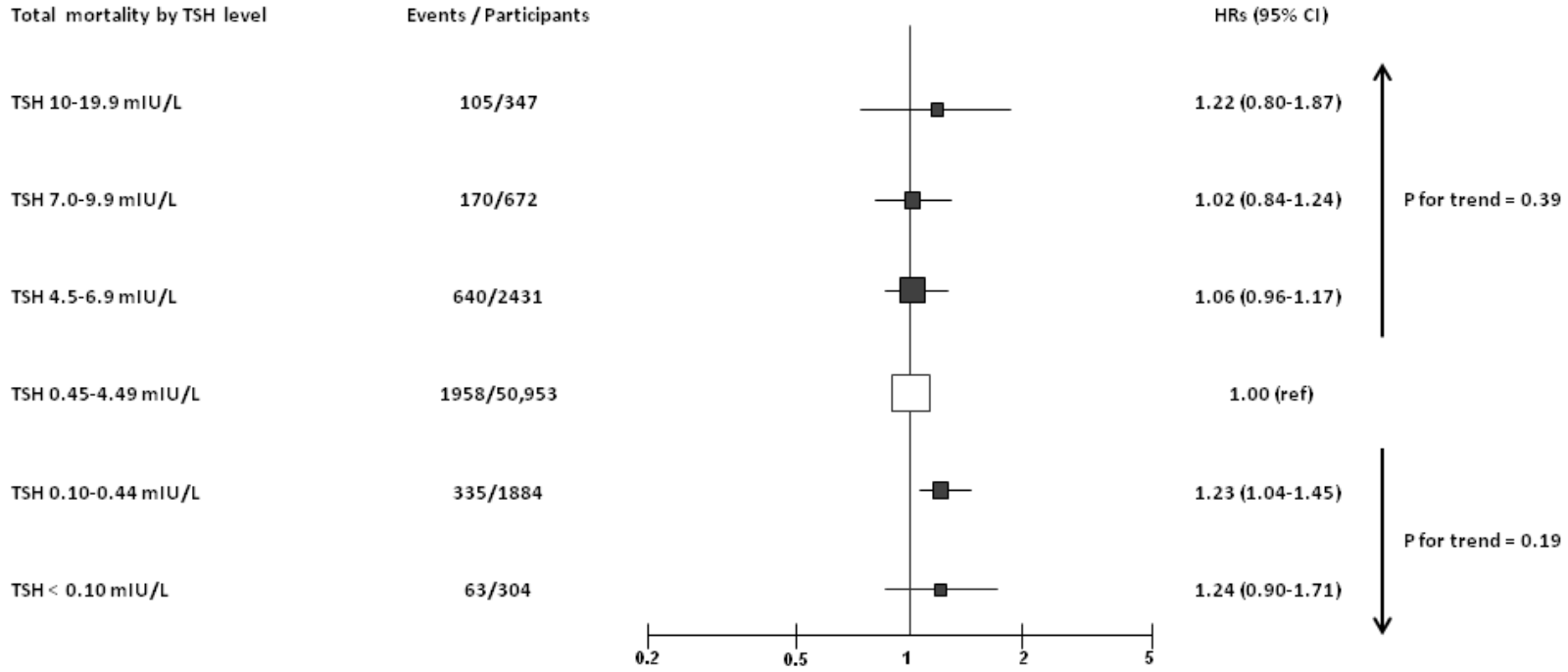
Abbreviations: NA, not available in the previous individual participant data analyses; CHD, coronary heart disease; HF, heart failure; HR, hazard ratio; CI, confidence intervals

**Table 2 The risk of CHD and HF events according to subclinical thyroid dysfunction compared to euthyroidism**

| Study | Description of study sample | CHD Events | | | HF Events | | |
|---|---|---|---|---|---|---|---|
| | | Euthyroidism | Subclinical hypothyroidism | Subclinical hyperthyroidism | Euthyroidism | Subclinical hypothyroidism | Subclinical hyperthyroidism |
| *United States* | | | HR (95% CI) | HR (95% CI) | | HR (95% CI) | HR (95% CI) |
| Cardiovascular Health Study (ref) | Community-dwelling adults with Medicare eligibility in 4 US communities | 1 (Ref) | 1.00 (0.85-1.17) | 1.12 (0.69-1.81) | 1 (Ref) | 0.91 (0.75-1.10) | 1.12 (0.64-1.93) |
| Health, Aging and Body Composition Study (ref) | Community-dwelling adults with Medicare eligibility in 2 US communities | 1 (Ref) | 0.89 (0.68-1.16) | 1.59 (0.90-2.83) | 1 (Ref) | 1.02 (0.74-1.39) | 0.84 (0.43-1.64) |
| *Europe* | | | | | | | |
| Birmingham Study (ref) | Community-dwelling adults aged ≥60 years from primary care practice in Birmingham, England | NA | NA | NA | NA | NA | NA |
| EPIC-Norfolk Study (ref) | Adults living in Norfolk, England | 1 (Ref) | 1.09 (0.89-1.33) | 1.12 (0.85-1.49) | 1 (Ref) | 1.39 (0.99-1.95) | 0.94 (0.53-1.66) |
| HUNT Study (ref) | Adults living in Nord-Trøndelag County, Norway | NA | NA | NA | NA | NA | NA |
| Leiden 85+ Study (ref) | All adults aged 85 years living in Leiden, the Netherlands | 1 (Ref) | 1.29 (0.59-2.80) | 1.37 (0.50-3.74) | 1 (Ref) | 1.00 (0.44-2.31) | 2.13 (0.98-4.63) |
| Pisa cohort (ref) | Patients admitted to cardiology department in Pisa, Italy [f] | 1 (Ref) | 1.72 (1.07-2.74) | 1.33 (0.79-2.22) | NA | NA | NA |
| Whickham Survey (ref) | Adults living in and near Newcastle upon Tyne, England | 1 (Ref) | 1.32 (0.89-1.96) | NA | NA | NA | NA |
| SHIP (ref) | Adults living in Western Pomerania, Germany | NA | NA | NA | NA | NA | NA |
| PROSPER study (ref) | Older community-dwelling adults at high cardiovascular risk in the Netherland, Ireland. and Scotland | NA | NA | NA | 1 (Ref) | 1.13 (0.70-1.83) | 2.81 (1.60-4.94) |
| Bari cohort (ref) | Outpatients with HF followed up by Cardiology Department in Bari, Italy | NA | NA | NA | 1 (Ref) | 3.12 (1.86-5.21) | 2.50 (0.78-8.03) |
| *Australia* | | | | | | | |
| Busselton Health Study (ref) | Adults living in Busselton, Western Australia | 1 (Ref) | 1.78 (1.22-2.58) | 1.15 (0.59-2.24) | NA | NA | NA |
| *Southern America* | | | | | | | |
| Brazilian Thyroid Study (ref) | Adults of Japanese descent living in São Paulo, Brazil | NA | NA | NA | NA | NA | NA |
| *Asia* | | | | | | | |
| Nagasaki Adult Health Study (ref) | Atomic bomb survivors in Nagasaki, Japan | NA | NA | NA | NA | NA | NA |
| **Overall** | | **1 (Ref)** | **1.18 (0.99-1.42)** | **1.21 (0.99-1.46)** | **1 (Ref)** | **1.26 (0.91-1.74)** | **1.46 (0.94-2.27)** |

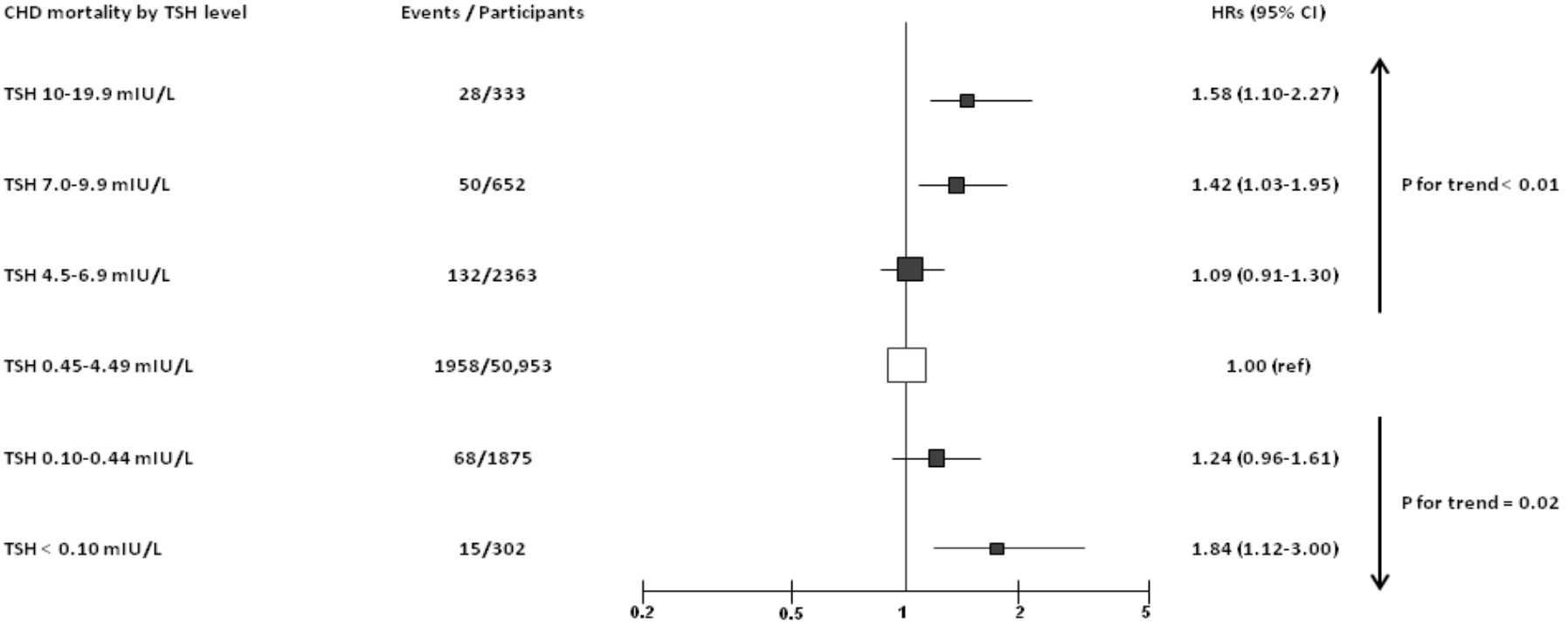
Abbreviations: NA, not available in the previous individual participant data analyses; CHD, coronary heart disease; HF, heart failure; HR, hazard ratio; CI, confidence intervals

**Figure 1** Hazard Ratios for Total Mortality According to Thyroid-Stimulating Hormone Levels



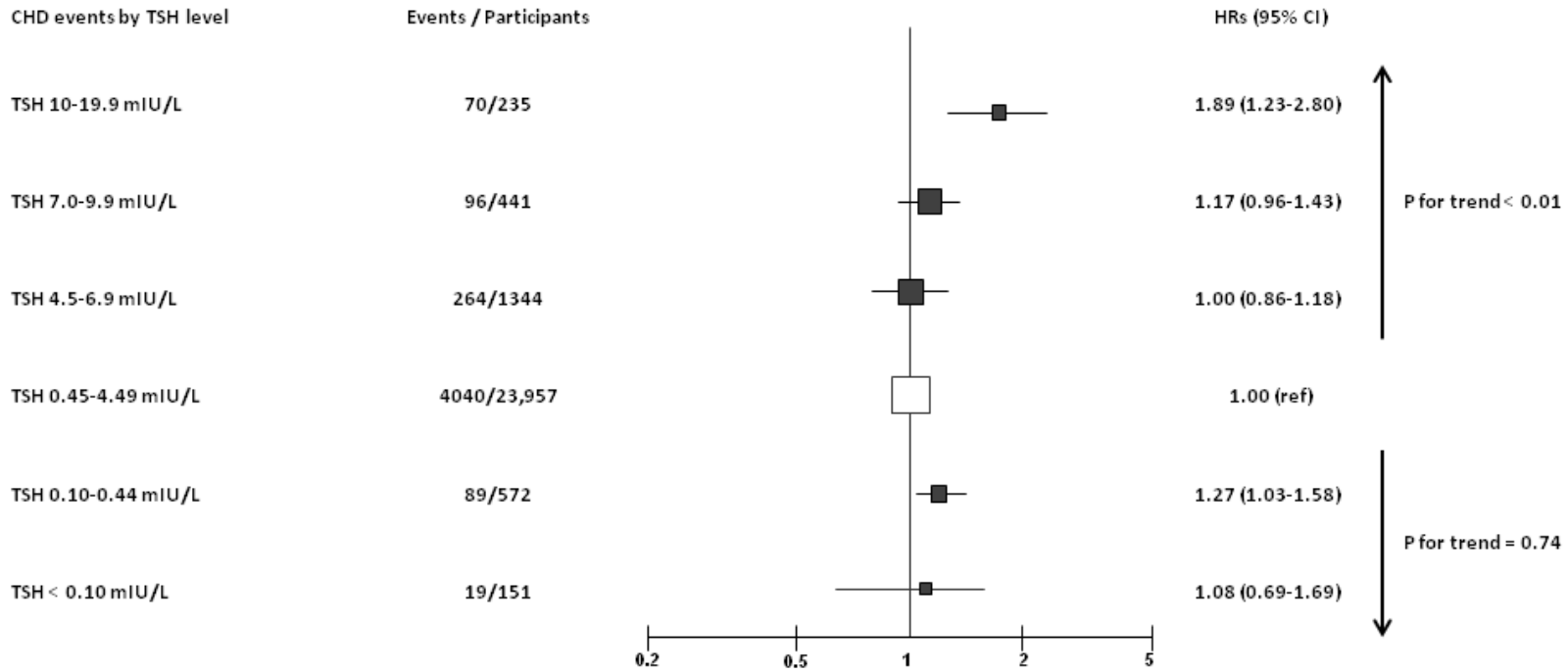

Abbreviations: CI: Confidence Interval; HR: Hazard Ratio; TSH: Thyroid-Stimulating Hormone.
Age- and gender-adjusted HRs and their 95% CI are represented by squares. Squares to the right of the solid lines indicate increased risk of HF events.

**Figure 2** Hazard Ratios for Coronary Heart Disease Mortality According to Thyroid-Stimulating Hormone Levels



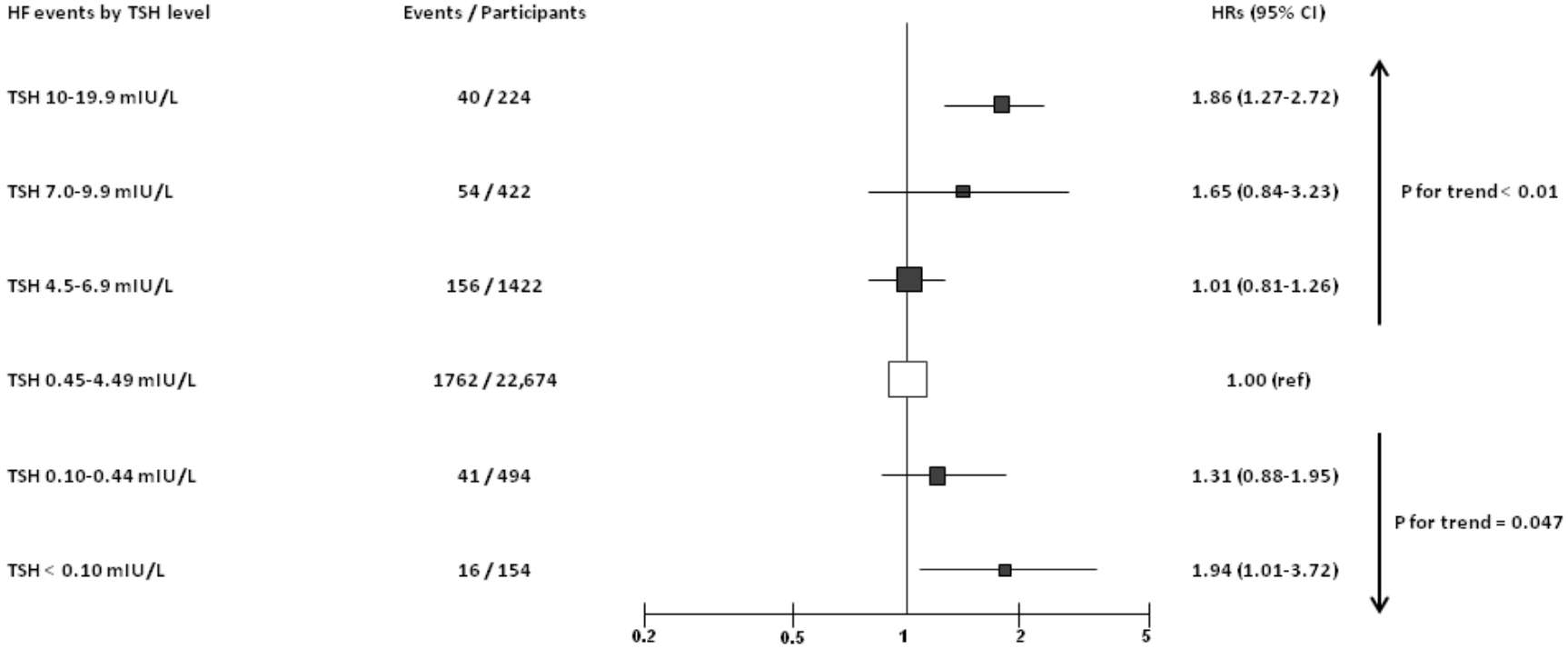

Abbreviations: CI: Confidence Interval; CHD : Coronary Heart Disease; HR: Hazard Ratio; TSH: Thyroid-Stimulating Hormone.
Age- and gender-adjusted HRs and their 95% CI are represented by squares. Squares to the right of the solid lines indicate increased risk of HF events.

**Figure 3** Hazard Ratios for Coronary Heart Disease Events According to Thyroid-Stimulating Hormone Levels




Abbreviations: CI: Confidence Interval; CHD: Coronary Heart Disease; HR: Hazard Ratio; TSH: Thyroid-Stimulating Hormone.
Age- and gender-adjusted HRs and their 95% CI are represented by squares. Squares to the right of the solid lines indicate increased risk of HF events.

**Figure 4** Hazard Ratios for Heart Failure Events According to Thyroid-Stimulating Hormone Levels




Abbreviations: CI: Confidence Interval; HF: Heart Failure; HR: Hazard Ratio; TSH: Thyroid-Stimulating Hormone.
Age- and gender-adjusted HRs and their 95% CI are represented by squares. Squares to the right of the solid lines indicate increased risk of HF events.

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