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The relation between thyroid function and anemia: a pooled analysis of individual participant data

Daisy M. Wopereis[1,2*], Robert S. Du Puy[1*], Diana van Heemst[2], John P. Walsh[3,4], Alexandra Bremner[5], Stephan J.L. Bakker[6], Douglas C. Bauer[7,8], Anne R. Cappola[9], Graziano Ceresini[10], Jean Degryse[11,12], Robin P.F. Dullaart[6], Martin Feller[13,14], Luigi Ferrucci[15], Carmen Floriani[13], Oscar H. Franco[16], Massimo Iacoviello[17], Georgio Iervasi[18], Misa Imaizumi[19], J. Wouter Jukema[20], Kay-Tee Khaw[21], Robert N. Luben[21], Sabrina Molinaro[22], Matthias Nauck[23], Kushang V. Patel[24], Robin P. Peeters[16,25], Bruce M. Psaty[26,27], Salman Razvi[28], Roger K. Schindhelm[29], Natasja M. van Schoor[30], David J. Stott[31], Bert Vaes[11,12], Mark P.J. Vanderpump[32], Henry Völzke[33], Rudi G.J. Westendorp[34], Nicolas Rodondi[13,14], Christa M. Cobbaert[35], Jacobijn Gussekloo[1,2], Wendy P.J. den Elzen[35] for the Thyroid Studies Collaboration.

1. Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, the Netherlands. 2. Department of Internal Medicine, section Gerontology and Geriatrics, Leiden University Medical Center, Leiden, the Netherlands. 3. Department of Endocrinology and Diabetes, Sir Charles Gairdner Hospital, Nedlands, Western Australia 4. Medical School, The University of Western Australia, Crawley, Western Australia. 5. School of Population Health, The University of Western Australia, Crawley, Western Australia. 6. Department of Internal Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands. 7. Department of Medicine, University of California, San Francisco, California, USA. 8. Department of Epidemiology and Biostatistics, University of California, San Francisco, California, USA. 9. Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA. 10. Department of Clinical and Experimental Medicine, Geriatric Endocrine Unit, University Hospital of Parma, Parma, Italy. 11. Institute of Health and Society, Université catholique de Louvain (UCL), Brussels, Belgium. 12. Department of Public Health and Primary Care, Katholieke Universiteit Leuven (KUL), Leuven, Belgium 13. Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland. 14. Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland. 15. National Institute on Aging, Baltimore, Maryland, USA. 16. Department of Epidemiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands. 17. University Cardiology Unit, Cardiothoracic Department, University Policlinic Hospital, Bari, Italy. 18. National Council Research Institute of Clinical Physiology/Tuscany Region G. Monasterio Foundation, Pisa, Italy. 19. Department of Clinical Studies, Radiation Effects Research Foundation, Nagasaki, Japan. 20. Department of Cardiology, Leiden University Medical Centre, Leiden, The Netherlands. 21. Department of Public Health and Primary Care, University of Cambridge, Cambridge, England. 22. National Council Research Institute of Clinical Physiology, Pisa, Italy. 23. Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Germany 24. Department of Anesthesiology and Pain Medicine, University of Washington, Seattle, Washington, USA. 25. Department of Internal Medicine, Rotterdam Thyroid Center, Erasmus Medical Center, Rotterdam, the Netherlands. 26. Cardiovascular Health Research Unit, Departments of Medicine, Epidemiology, and Health Services, University of Washington, Seattle, Washington, USA. 27. Kaiser Permanente Washington Health Research Institute, Seattle, Washington, USA. 28. Department of Endocrinology, Gateshead Health Foundation NHS Trust, Gateshead, England. 29. Department of Clinical Chemistry, Haematology and Immunology, Northwest Clinics, Alkmaar, the Netherlands. 30. Department of Epidemiology and Biostatistics, EMGO Institute for Health and Care Research, Amsterdam, the Netherlands. 31. Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom. 32. The Physicians' Clinic, Devonshire Street, London W1G 7AE, England. 33. Institute for Community Medicine, SHIP/Clinical-Epidemiological Research & German Centre of Cardiovascular Research, University of Greifswald, Greifswald, Germany. 34. Department of Public Health and Center of Healthy Aging, University of Copenhagen, Copenhagen, Denmark. 35. Department of Clinical Chemistry and Laboratory Medicine, Leiden University Medical Center, Leiden, the Netherlands.

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Context

Anemia and thyroid dysfunction often co-occur and both increase with age. Human data on the relationship between thyroid disease and anemia are scarce.

Objective

To investigate the cross-sectional and longitudinal associations between clinical thyroid status and anemia.
Design
Individual participant data meta-analysis.
Setting
Sixteen cohorts participating in the Thyroid Studies Collaboration (n=42 162).
Main outcome measures
Primary outcome measure was anemia (hemoglobin <130 g/L in men and <120 g/L in women).
Results
Cross-sectionally, participants with abnormal thyroid status had an increased risk of having anemia compared with euthyroid participants (overt hypothyroidism, pooled odds ratio 1.84 [95% CI: 1.35-2.50], subclinical hypothyroidism 1.21 [1.02-1.43], subclinical hyperthyroidism 1.27 [1.03-1.57], overt hyperthyroidism 1.69 [1.00-2.87]). Hemoglobin levels were lower in all groups compared to participants with euthyroidism.
In the longitudinal analyses (n=25,466 from 14 cohorts), the pooled hazard ratio for the risk of development of anemia was 1.38 [95% CI: 0.86-2.20] for overt hypothyroidism, 1.18 [1.00-1.38] for subclinical hypothyroidism, 1.15 [0.94-1.42] for subclinical hyperthyroidism and 1.47 [0.91-2.38] for overt hyperthyroidism. Sensitivity analyses excluding thyroid medication or high levels of C-reactive protein yielded similar results. No differences in mean annual change in hemoglobin levels were observed between the thyroid hormone status groups.
Conclusion
Higher odds of having anemia were observed in both participants with hypothyroid function and hyperthyroid function. In addition, reduced thyroid function at baseline showed a trend of increased risk of developing anemia during follow-up. It remains to be assessed in a randomized controlled trial whether treatment is effective in reducing anemia.

This individual participant data meta-analysis found higher odds of having anemia in both participants with decreased and increased thyroid function.

Introduction

Thyroid diseases and anemia are common disorders and their prevalences increase with age (1-4). Hypothyroidism and anemia can each cause non-specific symptoms of ill health like fatigue and both lead to decreased quality of life. The combination of anemia and abnormal thyroid function may therefore be accompanied by serious morbidity and further effects on quality of life.

The co-occurrence of anemia and hypothyroidism is not only a challenging diagnostic problem in allocating symptoms to one of the diseases, but may also point to a causal relationship between thyroid disease and anemia (5). Indeed, relationships between thyroid disease and anemia have already been documented in experimental animal studies in the distant past (5). For instance, hypophysectomized mammals were found to have decreased red blood cell counts that corrected after administration of thyroid hormones (6, 7). Additionally, mice deficient in the thyroid hormone receptor TRα have been found to have decreased hematocrit values (8).

However, human data regarding relationships between thyroid disease and hematologic anomalies are scarce. Researchers investigating potential altered erythropoiesis as a result of thyroid dysfunction found red cell abnormalities and a reduced proliferative potential of hematopoietic progenitor cells in both patients with hypo- and hyperthyroidism, but the total number of studied participants was low (9, 10).

In addition, a higher prevalence of anemia was identified in older male patients with subclinical hypothyroidism(11) and in patients with clinical hypothyroidism (12), but incidence estimates were not available due to the cross-sectional study design. Additionally, a rise of thyroid hormone levels or a decrease in levels of TSH within the reference ranges was associated with higher erythropoietic activity (13) but the low number of studied participants precluded stratification by hyperthyroid subgroups. In one population-based cohort both hypothyroidism and hyperthyroidism was associated with decreased hemoglobin in cross-sectional analyses but not in longitudinal analyses (14).

Clinical experimental evidence on the causal relation between low thyroid function and anemia is currently limited to a number of small case series, in which treatment of hypothyroidism with levothyroxine resulted in a significant increase in hemoglobin and resolution of anemia (12, 15, 16). Alternatively, and in line with the observational data, in a cohort of hyperthyroid patients a high prevalence of anemia was found, which returned to normal following antithyroid therapy (17).

Despite the myriad of smaller studies hinting at a potential relationship between thyroid dysfunction and anemia, methodologically sound pooled estimates drawn from large and representative populations are missing. With the current study we sought to determine the association between thyroid hormone status and anemia in cross-sectional and longitudinal analyses by performing an individual participant data meta-analysis on data from 16 independent observational cohort studies participating in the Thyroid Studies Collaboration.

Methods

Study population

We performed an individual participant data meta-analysis of cohorts participating in the Thyroid Studies Collaboration. The cohorts are summarized in table 1 and are described elsewhere in detail (2, 18-20). For the current project we included the 16 cohorts in which thyroid function tests and hemoglobin were measured at baseline.

Anemia

Anemia was defined according to the World Health Organization (WHO) criteria (hemoglobin concentration <130 g/L in men and <120 g/L in women) (21). In 14 cohorts, a follow-up measurement of hemoglobin was available.

Thyroid function

TSH and free T4 concentrations were measured at baseline in all cohorts. Cohort specific cut-off values were applied for free T4 concentrations (Appendix table 1). Participants with a TSH level of 0.45 to 4.5 mIU/L were categorized as euthyroid. Overt hypothyroidism was defined as a TSH level above 4.5 mIU/L in combination with reduced free T4 concentration. Subclinical hypothyroidism was defined as TSH level above 4.5 mIU/L in combination with a normal free T4 concentration. A TSH level below 0.45 mIU/L with normal free T4 levels was defined as subclinical hyperthyroidism. Overt hyperthyroidism was defined as TSH level below 0.45 mIU/L with an elevated free T4 concentration (2).

Statistical analyses

We performed a two-stage individual participant data meta-analysis to allow for consistent definitions and analyses across the cohorts, increased analytical flexibility and decreased complexity of the analyses (18, 22-25). In the first step, the cross-sectional and longitudinal associations between thyroid hormone status and anemia in each study cohort were estimated separately from supplied original study datasets with data on the participant level. In the second step all effect estimates found in step 1 were pooled using random-effects models (DerSimonian and Laird) with inverse variance weighting.

For the cross-sectional association between thyroid hormone status and anemia at baseline, logistic regression models were constructed. Prospectively, we investigated the risk of developing anemia during follow-up using Cox regression models; participants with pre-existing anemia were excluded. The analyses were based on the thyroid function category at baseline. If a new case of anemia was identified, it was assumed that the anemia had developed halfway through the follow-up period.

Thyroid status was included as a categorical variable (overt hypothyroidism, subclinical hypothyroidism, subclinical hyperthyroidism, overt hyperthyroidism), with euthyroidism as the reference group. All models were adjusted for age and sex. A p value for trend was obtained for both overt and subclinical hypothyroid and hyperthyroid categories. Subgroup analyses, including calculations of a p value for interaction, were performed separately for sex, age groups and ethnicity.

In sensitivity analyses, we excluded all participants who used antithyroid medication or thyroid hormone replacement therapy at baseline or during follow-up. We also compared mean hemoglobin levels at baseline between thyroid status groups and differences in mean annual change in hemoglobin levels during follow-up between thyroid status groups using linear regression models. Additionally we excluded all participants with a high level of C-reactive protein (CRP, >20 mg/L) as a proxy for chronic inflammatory disease.

Data analyses were performed using IBM SPSS Statistics Version 23 and Review Manager 5.3 from The Cochrane Collaboration.

Results

For this study, individual participant data of 56 297 participants from 16 different cohorts participating in the Thyroid Studies Collaboration were available. At baseline, thyroid function (TSH and fT4) and hemoglobin measurements were available from 42 162 participants, of whom 459 (1.1%) had overt hypothyroidism, 2930 (6.9%) had subclinical hypothyroidism, 36 081 (85.6%) were euthyroid, 2386 (5.7%) had subclinical hyperthyroidism, and 306 (0.7%) had overt hyperthyroidism.

Baseline characteristics of the cohorts are presented in Table 1. The overall median age of each cohort ranged from 46 to 85 years and the overall percentage of women was 51.0%. More detailed information about the study participants is presented in Appendix Tables 2 and 3. The participants excluded because their thyroid function or hemoglobin measurement were not available had a median ages ranging from 45 to 84; the percentage of women was 51.5%.

Cross-sectional analyses

At baseline 4274 (10.1%) participants had anemia; 15.9% in the overt hypothyroid group 11.6% in the subclinical hypothyroid group, 9.7% in the euthyroid group, 13.6% in the subclinical hyperthyroid group and 11.1% in the overt hyperthyroid group. Participants with subclinical or overt hypothyroidism and subclinical or overt hyperthyroidism had increased odds of having anemia compared to euthyroid participants (Table 2 and Figure 1). The pooled odds ratio for the overt hypothyroid group was 1.84 [95% CI: 1.35-2.50], 1.21 [1.02-1.43] for the group with subclinical hypothyroidism, 1.27 [1.03-1.57] for those with subclinical hyperthyroidism and 1.69 [1.00-2.87] for those in the overt hyperthyroid group. We observed statistically significant trends from euthyroidism to hypothyroidism (i.e. from subclinical hypothyroidism to overt hypothyroidism, p=0.01), and from euthyroidism to hyperthyroidism (i.e. from subclinical hyperthyroidism to overt hyperthyroidism, p=0.04). When the analyses were stratified by sex, we observed no statistically significant differences (all p values for interaction>0.05) between men and women, Table 2. Also, no statistically significant differences were observed between different age categories or between white, black or Asian participants.

Longitudinal analyses

In the longitudinal analyses 25 466 participants from 14 cohorts were included with a median follow-up time of 5.7 years (IQR 3.0-9.5). 2423 participants developed anemia during follow-up (14.9 per 1000 person years), 12.2% in the overt hypothyroid group, 12.0% in the subclinical hypothyroid group, 9.2% in the euthyroid group, 10.7% in the subclinical hyperthyroid group and 8.7% in the overt hyperthyroid group (Table 3 and Figure 2). The pooled hazard ratios for the risk of developing anemia were 1.38 [95% CI: 0.86-2.20] for the overt hypothyroid group, 1.18 [1.00-1.38] for the group with subclinical hypothyroidism, 1.15 [0.94-1.42] for the group with subclinical hyperthyroidism and 1.47 [0.91-2.38] in the overt hyperthyroid group. We observed a statistically significant trend from euthyroidism to hypothyroidism (p=0.02). No statistically significant trend was observed for euthyroidism to hyperthyroidism (p=0.20). When the participants were stratified by sex, age or ethnicity, these findings remained unchanged. Associations were more pronounced in those studies with a median follow-up ≥ 5 years (Appendix table 4).

Additional analyses

Cross-sectionally, hemoglobin levels (as a continuous variable) were lower (mean difference between -0.06 and -0.19 g/dL) in all groups compared to participants with euthyroidism (Appendix table 5). Prospectively, no differences in mean annual change in hemoglobin levels were observed between the thyroid hormone status groups (Appendix table 6). Similar results were observed when analyses were stratified on sex. In addition, sensitivity analyses excluding participants who used thyroid hormone medication or with high levels of CRP, yielded higher odds ratios in line with the unrestricted results but with wider confidence intervals (Appendix Table 7 and 8).

For all main analyses I^2 statistics remained below 40% (Appendix Table 9 and 10) and, in combination with size and direction of effects, statistical heterogeneity was deemed low to negligible (26).

Discussion

In this individual participant data meta-analysis, we observed a cross-sectional relation between thyroid function and anemia; higher odds of anemia were observed in both participants with overt and subclinical hypothyroidism as well as overt and subclinical hyperthyroidism. In addition, reduced thyroid function at baseline showed a trend of increased risk of developing anemia during follow-up. The longitudinal association between overt and subclinical hyperthyroidism and the risk of developing anemia did not reach statistical significance. Prospectively, no differences in mean annual change in hemoglobin levels were observed between the thyroid hormone status groups.

The findings in the current individual participant data meta-analysis build on findings from earlier studies where thyroid dysfunction was associated with abnormal red blood cell indices (11-13). In this study thyroid dysfunction, whether overt or subclinical hypo- and hypothyroidism, was associated with slightly lower hemoglobin levels. Given the small difference in hemoglobin levels between thyroid function groups, the contribution of thyroid dysfunction on low hemoglobin levels or anemia may be small. It remains to be assessed in a randomized controlled trial whether treatment of (subclinical) hypothyroidism is effective in reducing anemia to further decide whether the findings are thought to be clinically relevant and whether these should influence practice and policies. Christ-Crain and colleagues showed that erythropoietin levels increased after thyroxin treatment in patients with subclinical hypothyroidism (27). In addition, a number of studies have also shown a beneficial effect of thyroid hormone treatment in patients with hypothyroidism on erythropoietin levels (12, 15, 16).

There are numerous types of anemia that can be classified according to whether the anemia is primarily the result of blood loss, deficits in the production of healthy erythrocytes or by reduced erythrocyte survival. Currently it is unclear what mechanisms exactly allow thyroid function and erythropoiesis to be linked pathophysiologically, and how both ends of the thyroid disease spectrum might lead to an anemic state. However, for subclinical and overt hyperthyroidism several pathways have been proposed. Hyperthyroidism might be associated with anemia via reduced erythrocyte survival due to altered iron metabolism and utilization, enhanced oxidative stress and increased haemolysis (28, 29). Thyroid hormones stimulate energy metabolism, resulting in an enhanced requirement of oxygen delivery to the tissues speeding up destructive processes.

For subclinical and overt hypothyroidism there is accumulating evidence that indicates low thyroid function may be causally related to anemia via deficits in the production of healthy erythrocytes, although the underlying mechanisms by which thyroid hormones and TSH may lead to anemia are not fully understood (30). Triiodothyronine (T3), thyroxine (T4) and thyroid stimulating hormone (TSH), may play a direct role in erythropoiesis (31). For instance, both T3 and T4 are involved in the regulation of hematopoiesis by influencing erythroid precursor proliferative capacity (32). In addition, a direct β2-adrenergic receptor-mediated stimulation of red cell precursors by T4 has been shown (33). T4 has also been found to stimulate the initiation and completion of hemoglobin protein chains in vitro , and to enhance red blood cell formation (5). Thyroid hormones were also shown to promote erythropoiesis by increasing the production of erythropoietin by the kidneys (34). Furthermore, there is evidence that thyroid hormones affect iron transport and utilisation. TSH could affect hematopoiesis by binding to a functional thyrotropin receptor (TSHR), which can be found in erythrocytes and some extrathyroidal tissues (10). Another explanation for the co-occurrence of low thyroid function and anemia is that there are common causes for abnormal thyroid status and anemia. Chronic (inflammatory) diseases, malnutrition and malabsorption may all result in reduced thyroid status as an adaptive response to energetic deficits. In addition, malnutrition and malabsorption may cause deficiencies of micronutrients that are crucial for erythropoiesis, like iron, vitamin B12 and folate, as well as iodine deficiency which is crucial for normal thyroid function. Interestingly, iron deficiency, which is the most common cause of anemia, was also found to decrease the activity of TPO, an iron-containing enzyme involved in the synthesis of thyroid hormones (35).

Strengths of the current individual participant data meta-analysis are the inclusion of individual participant data of large cohort studies from across the globe. The availability of individual participant data allowed us to choose clinically relevant categories of thyroid function and anemia, to standardize these definitions, and to perform several standardized subgroup analyses.

An individual participant data meta-analysis of well-designed observational studies can be considered an important tool in assessing causality. When studying causality, the nine considerations of Austin Bradford Hill in 1965 can be used as a checklist (36). In our study, many of these considerations are met. Although the individual study cohorts and individual subgroups may have been small, we had sufficient power to study the associations in this pooled analysis because of the increased combined sample size. Since multiple studies were included, we could also study consistency in the results of the different cohorts (e.g. effect estimates all pointing in the same direction); the low level of heterogeneity also aids in considering a causal relation. In addition, the availability of the individual participant data allowed us to define identical subgroups for each study in a biological gradient, from overt hypothyroidism to overt hyperthyroidism. The availability of prospective observational data is also in compliance with the fourth consideration of temporality; in 14 studies a baseline measurement of the determinant (thyroid function) and (baseline and) follow-up

measurements of the outcome of interest (hemoglobin) were available. Therefore, our pooled analysis of observational studies satisfies multiple criteria of Bradford Hill. However, it remains to be assessed in a well-designed randomized controlled trial with a considerable number of participants with (subclinical) hypothyroidism, if treatment is effective in reducing anemia. Further analysis of the data from two well-designed RCT's for subclinical hypothyroidism in older persons (TRUST & IEMO Thyroid Trial (37, 38)) could be a first attempt at uncovering the clinical relevance of thyroid influences on hemoglobin levels.

Some limitations of this study have to be acknowledged as well. First, a limitation of this pooled analysis is that TSH and free T4 were only measured once at baseline. Because subclinical hypothyroidism has been shown to normalize in one third of cases (39), in guidelines it is often recommended that measurements of these parameters are repeated. Unfortunately, repeated TSH and free T4 measurements were not available in many cohorts. Erroneously classifying euthyroid patients on the basis of one measurement may have led to an underestimation of the associations found. Second, the statistical power was more limited in the longitudinal models than in the baseline, cross-sectional analysis. The association between overt and subclinical hyperthyroidism and the risk of developing anemia did not reach statistical significance, but the results of the longitudinal analyses followed a similar pattern. Third, we did not apply age-adjusted reference ranges as per current consensus and usual practice. However, evidence in favour of age-specific TSH reference ranges is starting to accumulate (40), so too is evidence to the contrary (41-43). This is an important topic of future research. Fourth, we performed sensitivity analyses excluding participants with high CRP levels as a proxy for chronic diseases that might predispose to anemia, but this only excluded diseases associated with inflammation. Particularly in the group of participants with subclinical hypothyroidism the possibility of the presence of non-thyroidal illness cannot be fully excluded. As a result, possible residual errors caused by residual bias and confounding may have deflated the results. Unfortunately information on additional potential confounding factors, like thyroid medication dose titrations, other diseases relating to anemia (cancer, chronic kidney disease, leukemia, gastric ulcers, arthritis or COPD), menopausal state, non-thyroidal illness, concomitant medications and iron or vitamin supplements, was not available for most cohorts.

In conclusion, we observed higher odds of anemia in both participants with hypothyroid function and hyperthyroid function. In addition, reduced thyroid function at baseline showed a trend of increased risk of developing anemia during follow-up. It remains to be assessed in a randomized controlled trial whether treatment of (subclinical) hypothyroidism is effective in reducing anemia.

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*Authors contributed equally.

Correspondence and reprint requests: Wendy den Elzen, Department of Clinical Chemistry and Laboratory Medicine, Leiden University Medical Center, Post Zone E2-P, PO Box 9600, 2300 RC Leiden, the Netherlands. E-mail: w.p.j.den_elzen@lumc.nl

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Figure 1. The pooled odds ratios of the risk of having anemia at baseline with the 95% confidence interval and the p value for trend. Logistic regression models corrected for age and sex; reference group is euthyroidism.

Figure 2. The pooled hazard ratios of developing anemia during follow-up in the thyroid function groups with the 95% confidence interval and the p value for trend. Cox regression models corrected for age and sex; reference group is euthyroidism.

Table 1. Baseline characteristics of individuals in included studies (N=42 162)

Study	Study population	Total number of participants: baseline/follow-up	Age, Median (Range), y	Women (%)	Antithyroid or thyroid medication at baseline (%)	Anemia at baseline (%)	Anemia during follow-up (%)	Duration of follow-up, Median (IQR), y	Total person years
Total		42 162/25 466	14-103	22 308 (52.9)	1067 (2.5)	4274 (10.1)	2423 (5.7)	5.7 (3-9.5)	162583
Bari study	Outpatients with heart failure followed up by Cardiology Department in Bari, Italy	337/206	66 (21-92)	78 (20.5)	23 (6.8)	69 (20.5)	30 (8.9)	1.4 (0.7-1.9)	273
BELFRAIL	Subjects aged 80 years and older in three well-circumscribed areas of Belgium.	524/331	84 (80-100)	331 (63.2)	52 (9.9)	106 (20.2)	52 (9.9)	1.6 (1.4-1.8)	521
Busselton Health study	Adults living in Busselton, Western Australia	2074/1245	51 (17-90)	1030 (49.7)	27 (1.3)	76 (3.7)	54 (2.6)	14.0 (14.0-14.0)	17164
Cardiovascular Health study	Community-dwelling adults with Medicare eligibility in 4 US	3106/2314	71 (64-100)	1864 (60.0)	0	259 (8.3)	321 (10.3)	3.0 (3.0-3.0)	12552

	communities.								
EPIC-Norfolk study	Adults aged 45-79 years living in Norfolk, England	13 1/27	59 (40-78)	7276 (54.8)	NA	1090 (8.2)	499 (3.8)	4.3 (3.4-12.3)	57604
Health, Aging, and Body Composition study	Community dwelling adults aged 70-79 years with Medicare eligibility in 2 US communities	2531/1236	74 (70-81)	1305 (51.6)	253 (10.0)	384 (15.2)	195 (7.7)	7.5 (7.5-7.5)	8543
InChianti study	Community dwelling from two small towns in Tuscany, Italy. Invecchiare in Chianti, "Aging in the Chianti Area" (InCHIANTI) study.	1200/944	72 (21-103)	675 (56.3)	30 (2.5)	120 (10.0)	177 (14.8)	9.0 (6.0-9.2)	6958
Longitudinal Aging Study Amsterdam (LASA)(20)	Random sample of older men and women (aged 55-85) in Amsterdam, Zwolle, and Oss, the Netherlands.	766/329	68 (55-85)	393 (51.3)	14 (1.8)	43 (5.6)	28 (3.7)	3.0 (3.0-3.1)	974
Leiden 85-plus Study	All adults aged 85 years living in Leiden, the Netherlands.	555/397	85 (NA)	368 (66.3)	20 (3.6)	158 (28.5)	98 (17.7)	3.0 (0.5-5.0)	1324
Nagasaki Adult Health study	Atomic bomb survivors in Nagasaki, Japan.	965/753	57 (38-92)	578 (59.9)	11 (1.1)	179 (18.5)	196 (20.3)	11.9 (7.4-12.0)	7196
Pisa cohort	Patients admitted to cardiology department in Pisa, Italy.	2259/NA	68 (14-96)	785 (34.7)	NA	490 (21.7)	NA	NA	NA
PREVEND study	Inhabitants, aged 28–75 years, of the city of Groningen, The Netherlands.	934/779	60 (35-82)	397 (42.5)	NA	106 (11.3)	82 (8.8)	5.7 (5.7-5.7)	8247
PROSPER study	Older community dwelling adults at high cardiovascular risk in the Netherlands, Ireland, and Scotland.	5769/5138	75 (69-83)	2983 (51.7)	256 (4.4)	402 (7.0)	203 (3.5)	0.25 (0.25-0.25)	1261
Rotterdam Study	All inhabitants of the suburb Ommoord in Rotterdam, the Netherlands, aged 55 years and over.	1835/1322	69 (55-93)	1135 (61.9)	45 (2.5)	109 (5.9)	214 (11.7)	11.1 (6.6-17.4)	14066
SHIP(44)	Adults living in Western Pomerania, Germany.	4214/2882	50 (20-81)	2139 (50.8)	263 (6.2)	589 (14.0)	274 (6.5)	10.0 (5.0-11.0)	25900
Whickham Survey	Adults living in and near	1807/NA	46 (18-93)	971 (53.7)	73 (4.0)	94 (5.2)	NA	NA	NA

	Newcastle upon Tyne, England.								

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

Table 2. The risk of having anemia at baseline according to thyroid hormone status (N=42 162 from 16 cohorts).

	Overt hypothyroidism	Subclinical hypothyroidism	Euthyroidism	Subclinical hyperthyroidism	Overt hyperthyroidism	N overt hypo/subcl hypo/subcl hyper/overt hyper
Pooled OR[a] (95% CI)						
All[*]	1.84 (1.35-2.50)	1.21 (1.02-1.43)	1 (ref)	1.27 (1.03-1.57)	1.69 (1.00-2.87)	459/2930/36081/2386/306
Sex						
Male	2.45 (1.45-4.12)	1.27 (1.03-1.57)	1 (ref)	1.19 (0.95-1.49)	1.59 (0.80-3.14)	122/1029/17546/1055/102
Female	1.79 (1.30-2.47)	1.23 (0.99-1.52)	1 (ref)	1.42 (1.11-1.81)	1.78 (0.99-3.21)	337/1901/18535/1331/204
Age						
<50 years[e]	2.25 (1.10-4.60)	1.15 (0.77-1.74)	1 (ref)	1.27 (0.73-2.21)	3.53 (0.26-48.39)	48/452/6763/599/27
50-65 years	5.53 (0.93-33.03)	1.44 (0.94-2.21)	1 (ref)	1.88 (1.09-3.24)	4.71 (1.25-17.78)	132/677/9719/670/63
65-80 years	2.02 (1.02-3.99)	1.40 (1.10-1.78)	1 (ref)	1.21 (0.85-1.73)	1.49 (0.89-2.51)	215/1711/16814/949/186
>80 years	1.91 (1.01-3.62)	1.03 (0.68-1.54)	1 (ref)	1.49 (0.99-2.23)	2.66 (0.35-20.26)	65/234/2646/168/27
Ethnicity						
White[f]	1.97 (1.37-2.82)	1.29 (1.11-1.51)	1 (ref)	1.30 (1.04-1.63)	1.56 (1.03-2.34)	431/2687/34154/2339/303
Black[b]	0.96 (0.20-4.58)	1.51 (0.74-3.05)	1 (ref)	0.77 (0.31-1.89)	-	12/98/1013/35/2
Asian[c]	2.01 (0.63-6.39)	0.87 (0.54-1.39)	1 (ref)	0.82 (0.10-6.83)	-	13/143/828/8/1
Other[d]	-	-	1 (ref)	-	-	0/0/22/1/0

[*] P for trend; overt hyperthryroidism to euthyroidism p=0.01; euthyroidism to overt hyperthyroidism p=0.04
[ǂ] P value for interaction (p<0.05)
[a] Results were obtained by logistic regression analysis, adjusted for age (if applicable) and sex
[b] Only data from CHS, HABC and PREVEND
[c] Only data from LASA, Nagasaki, PREVEND and Rotterdam
[d] Only data from LASA, PREVEND and Rotterdam
[e] Reference group is <50 years
[f] Reference group is White

Table 3. The risk of developing anemia during follow-up according to thyroid hormone status at baseline (N = 25 466 from 14 cohorts).

	Overt hypothyroidism	Subclinical hypothyroidism	Euthyroidism	Subclinical hyperthyroidism	Overt hyperthyroidism	N overt hypo/subcl hypo/subcl hyper/ overt hyper
Pooled HR[a] (95% CI)						
All[*]	1.38 (0.86-2.20)	1.18 (1.00-1.38)	1 (ref)	1.15 (0.94-1.42)	1.47 (0.91-2.38)	270/1678/21965/1358/195
Sex						
Male	2.14 (0.79-5.79)	1.05 (0.83-1.34)	1 (ref)	1.41 (0.92-2.18)	0.83 (0.26-2.61)	62/577/10450/584/63
Female	1.19 (0.75-1.88)	1.37 (1.05-1.80)	1 (ref)	1.22 (0.95-1.57)	2.27 (1.30-3.93)	207/1096/11487/773/131
Age						
<50 years[e]	17.81 (4.06-78.24)	1.48 (0.78-2.83)	1 (ref)	1.09 (0.68-1.73)	-	16/106/3857/343/21
50-65 years	1.58 (0.14-18.00)	1.14 (0.82-1.58)	1 (ref)	1.02 (0.70-1.50)	2.97 (0.56-15.64)	85/384/5872/414/32
65-80 years	1.39 (0.81-2.37)[ǂ]	1.20 (0.96-1.51)	1 (ref)	1.14 (0.83-1.57)	1.51 (0.85-2.69)	130/1069/10737/521/124
>80 years	1.48 (0.55-4.03)[ǂ]	1.30 (0.80-2.10)	1 (ref)	1.57 (0.98-2.50)	3.59 (0.49-26.06)	39/119/1499/80/18
Ethnicity						
White[f]	1.38 (0.75-2.54)	1.21 (1.00-1.45)	1 (ref)	1.16 (0.93-1.44)	1.52 (0.93-2.50)	257/1527/20849/1336/193
Black[b]	2.80 (0.38-	1.30 (0.59-2.83)	1 (ref)	1.57 (0.57-4.36)	-	5/41/415/16/1

	20.76)					
Asian[c]	1.68 (0.53-5.29)	1.03 (0.70-1.51)	1 (ref)	-	-	6/109/654/6/1
Other[d]	-	-	1 (ref)	-	-	0/0/12/0/0

[*] P for trend; overt hyperthryroidism to euthyroidism p=0.02; euthyroidism to overt hyperthyroidism p=0.20
[ǂ] P value for interaction (p<0.05)
[a]Results were obtained by cox regression analysis, adjusted for age (if applicable) and sex
[b]Only data from CHS, HABC and PREVEND
[c]Only data from LASA, Nagasaki, PREVEND and Rotterdam
[d]Only data from LASA, PREVEND and Rotterdam
[e]Reference group is <50 years
[f]Reference group is White