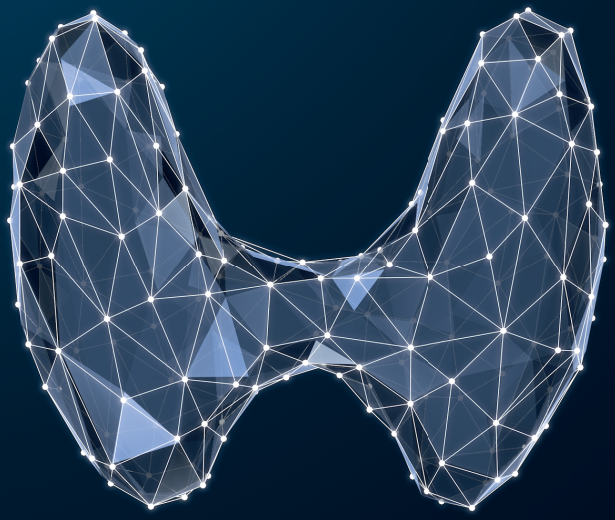
Subclinical hypothyroidism in community-dwelling older people: consequences and treatment outcomes

Du Puy, R.S.



Chapter 4

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

Daisy M Wopereis
Robert S Du Puy
Diana van Heemst
John P Walsh
Alexandra Bremner
Stephan J L Bakker
Douglas C Bauer
Anne R Cappola
Graziano Ceresini
Jean Degryse
Robin PF Dullaart
Martin Feller
Luigi Ferrucci
Carmen Floriani
Oscar H Franco
Massimo Iacoviello
Georgio Iervasi
Misa Imaizumi
J Wouter Jukema
Kay-Tee Khaw
Robert N Luben
Sabrina Molinaro
Matthias Nauck
Kushang V Patel
Robin P Peeters
Bruce M Psaty
Salman Razvi
Roger K Schindhelm
Natasja M van Schoor
David J Stott
Bert Vaes
Mark PJ Vanderpump
Henry Völzke
Rudi GJ Westendorp
Nicolas Rodondi
Christa M Cobbaert
Jacobijn Gussekloo
Wendy PJ den Elzen for the

Thyroid Studies Collaboration

The Journal of Clinical Endocrinology & Metabolism, 2018;103(10):3658-3667

DOI: 10.1210/jc.2018-00481

ABSTRACT

Context

Anaemia and thyroid dysfunction often co-occur, and both increase with age. Human data on relationships between thyroid disease and anaemia are scarce.

Objective

To investigate the cross-sectional and longitudinal associations between clinical thyroid status and anaemia.

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 anaemia (haemoglobin < 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 anaemia compared with euthyroid participants [overt hypothyroidism, pooled OR 1.84 (95% CI 1.35 to 2.50), subclinical hypothyroidism 1.21 (1.02 to 1.43), subclinical hyperthyroidism 1.27 (1.03 to 1.57), and overt hyperthyroidism 1.69 (1.00 to 2.87)]. Haemoglobin levels were lower in all groups compared with participants with euthyroidism. In the longitudinal analyses (N = 25,466 from 14 cohorts), the pooled hazard ratio for the risk of development of anaemia was 1.38 (95% CI 0.86 to 2.20) for overt hypothyroidism, 1.18 (1.00 to 1.38) for subclinical hypothyroidism, 1.15 (0.94 to 1.42) for subclinical hyperthyroidism, and 1.47 (0.91 to 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 haemoglobin levels were observed between the thyroid hormone status groups.

Conclusion

Higher odds of having anaemia were observed in participants with both hypothyroid function and hyperthyroid function. In addition, reduced thyroid function at baseline showed a trend of increased risk of developing anaemia during follow-up. It remains to be assessed in a randomised controlled trial whether treatment is effective in reducing anaemia.

INTRODUCTION

Thyroid diseases and anaemia are common disorders, and their prevalence increases with age.[1-4] Hypothyroidism and anaemia can each cause nonspecific symptoms of ill health like fatigue, and both lead to decreased quality of life. The combination of anaemia and abnormal thyroid function may therefore be accompanied by serious morbidity and further effects on quality of life.

The co-occurrence of anaemia 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 anaemia.[5] Indeed, relationships between thyroid disease and anaemia have already been documented in experimental animal studies in the distant past. [5] For instance, hypophysectomised 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 haematocrit 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 hypothyroidism and hyperthyroidism, but the total number of studied participants was low.[9,10]

In addition, a higher prevalence of anaemia 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 were associated with decreased haemoglobin in cross-sectional analyses but not in longitudinal analyses.[14]

Clinical experimental evidence on the causal relation between low thyroid function and anaemia is currently limited to a number of small case series in which treatment of hypothyroidism with levothyroxine resulted in a considerable increase in haemoglobin and resolution of anaemia.[12,15,16] Alternatively, and in line with the observational data, in a cohort of patients with hyperthyroidism, a high prevalence of anaemia 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 anaemia, methodologically sound pooled estimates drawn from large and representative populations are missing. In the current study, we sought to determine the association between thyroid hormone status and anaemia 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 summarised in Table 1 and described elsewhere in detail.[4,18-21] For the current project, we included the 16 cohorts in which thyroid function tests and haemoglobin were measured at baseline.

Anaemia

Anaemia was defined according to the World Health Organization criteria (haemoglobin concentration < 130 g/L in men and < 120 g/L in women).[22] In 14 cohorts, a follow-up measurement of haemoglobin 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 (Supplemental Table 1). Participants with a TSH level of 0.45 to 4.5 mIU/L were categorised as euthyroid. Overt hypothyroidism was defined as a TSH level > 4.5 mIU/L in combination with reduced free T4 concentration. Subclinical hypothyroidism was defined as a TSH level > 4.5 mIU/L in combination with a normal free T4 concentration. A TSH level < 0.45 mIU/L with normal free T4 levels was defined as subclinical hyperthyroidism. Overt hyperthyroidism was defined as a TSH level < 0.45 mIU/L with an elevated free T4 concentration.[4]

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.[18,23-26] In the first step, the cross-sectional and longitudinal associations between thyroid hormone status and anaemia 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 one were pooled using random-effects models (DerSimonian and Laird) with inverse variance weighting.

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

Thyroid status was included as a categorical variable (overt hypothyroidism, subclinical hypothyroidism, subclinical hyperthyroidism, and 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 haemoglobin levels at baseline between thyroid status groups and differences in mean annual change in haemoglobin 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 free T4) and haemoglobin measurements were available from 42,162 participants, of whom 459 (1.1%) had overt hypothyroidism, 2,930 (6.9%) had subclinical hypothyroidism, 36,081 (85.6%) were euthyroid, 2,386 (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 Supplemental Tables 2 and 3. The participants excluded because their thyroid function or haemoglobin measure-

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 (%)	Anaemia at baseline (%)	Anaemia during follow-up (%)	Duration of follow-up, Median (IQR), y	Total person years
Total		42,162/25,466	14-103	22,308 (52.9)	1,067 (2.5)	4,274 (10.1)	2,423 (5.7)	5.7 (3-9.5)	162,583
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	2,074/1245	51 (17-90)	1,030 (49.7)	27 (1.3)	76 (3.7)	54 (2.6)	14.0 (14.0-14.0)	17,164
Cardiovascular Health study	Community-dwelling adults with Medicare eligibility in 4 US communities.	3,106/2314	71 (64-100)	1,864 (60.0)	0	259 (8.3)	321 (10.3)	3.0 (3.0-3.0)	12,552
EPIC-Norfolk study	Adults aged 45-79 years living in Norfolk, England	13 1/27	59 (40-78)	7,276 (54.8)	NA	1,090 (8.2)	499 (3.8)	4.3 (3.4-12.3)	57,604
Health, Aging, and Body Composition study	Community dwelling adults aged 70-79 years with Medicare eligibility in 2 US communities	2,531/1236	74 (70-81)	1,305 (51.6)	253 (10.0)	384 (15.2)	195 (7.7)	7.5 (7.5-7.5)	8,543
InChianti study	Community dwelling from two small towns in Tuscany, Italy. Invecchiare in Chianti, "Aging in the Chianti Area" (InCHIANTI) study.	1,200/944	72 (21-103)	675 (56.3)	30 (2.5)	120 (10.0)	177 (14.8)	9.0 (6.0-9.2)	6,958
Longitudinal Aging Study Amsterdam (LASA)	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)	1,324
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)	7,196

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

Study	Study population	Total number of participants: baseline/ follow-up	Age, Median (Range), y	Women (%)	Antithyroid or thyroid medication at baseline (%)	Anaemia at baseline (%)	Anaemia during follow-up (%)	Duration of follow-up, Median (IQR), y	Total person years
Pisa cohort	Patients admitted to cardiology department in Pisa, Italy.	2,259/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)	8,247
PROSPER study	Older community dwelling adults at high cardiovascular risk in the Netherlands, Ireland, and Scotland.	5,769/5138	75 (69-83)	2,983 (51.7)	256 (4.4)	402 (7.0)	203 (3.5)	0.25 (0.25-0.25)	1,261
Rotterdam Study	All inhabitants of the suburb Ommoord in Rotterdam, the Netherlands, aged 55 years and over.	1,835/1322	69 (55-93)	1,135 (61.9)	45 (2.5)	109 (5.9)	214 (11.7)	11.1 (6.6-17.4)	14,066
SHIP	Adults living in Western Pomerania, Germany.	4,214/2882	50 (20-81)	2,139 (50.8)	263 (6.2)	589 (14.0)	274 (6.5)	10.0 (5.0-11.0)	25,900
Whickham Survey	Adults living in and near Newcastle upon Tyne, England.	1,807/NA	46 (18-93)	971 (53.7)	73 (4.0)	94 (5.2)	NA	NA	NA

Abbreviations: EPIC, European Prospective Investigation of Cancer; Health ABC, Health, Aging and Body Composition; IQR, interquartile range (25th–75th percentiles); NA, not available; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; SHIP, Study of Health in Pomerania.

ment were not available had a median age ranging from 45 to 84 years; the percentage of women was 51.5%.

Cross-sectional analyses

At baseline, 4,274 (10.1%) participants had anaemia: 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 anaemia compared with participants with euthyroidism (Table 2; Figure 1). The pooled OR for the overt hypothyroid group was 1.84 (95% CI 1.35 to 2.50), 1.21 (1.02 to 1.43) for the group with subclinical hypothyroidism, 1.27 (1.03 to 1.57) for those with subclinical hyperthyroidism, and 1.69 (1.00 to 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 noteworthy differences were observed among different age categories or among white, black, or Asian participants.

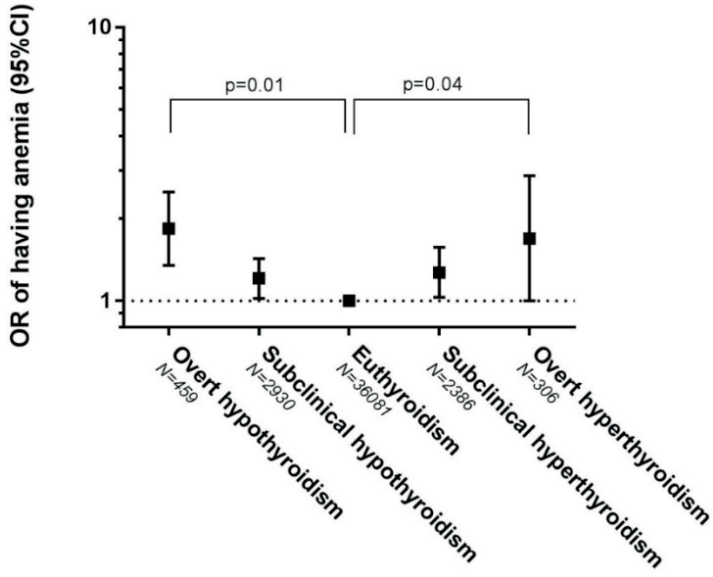


Figure 1. The pooled ORs of the risk of having anaemia at baseline with the 95% CI and p value for trend. Logistic regression models corrected for age and sex; reference group is euthyroidism.

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

	Overt Hypothyroidism	Subclinical Hypothyroidism	Euthyroidism	Subclinical Hyperthyroidism	Overt Hyperthyroidism	N Overt Hypothyroidism/ Subclinical Hypothyroidism/ Subclinical Hyperthyroidism/ Overt Hyperthyroidism
All[a]	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)	459/2,930/36,081/2,386/306
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)	122/1,029/17,546/1,055/102
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)	337/1,901/18,535/1,331/204
Age, y						
< 50[b]	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)	48/452/6,763/599/27
50-65	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)	132/677/9,719/670/63
65-80	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)	215/1,711/16,814/949/186
> 80	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)	65/234/2,646/168/27
Ethnicity						
White[c]	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)	431/2,687/34,154/2,339/303
Black[d]	0.96 (0.20-4.58)	1.51 (0.74-3.05)	1 (ref)	0.77 (0.31-1.89)	-	12/98/1,013/35/2
Asian[e]	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[f]	-	-	1 (ref)	-	-	0/0/22/1/0

Data are pooled hazard ratio (95% CI) unless otherwise noted. Results were obtained by logistic regression analysis, adjusted for age (if applicable) and sex.

[a] p for trend: overt hyperthyroidism to euthyroidism, p=0.01; euthyroidism to overt hyperthyroidism p=0.04

[b] Reference group is < 50 y.

[c] Reference group is white.

[d] Only data from CHS, HEALTH ABC and PREVEND.

[e] Only data from LASA, Nagasaki, PREVEND and Rotterdam.

[f] Only data from LASA, PREVEND and Rotterdam.

Longitudinal analyses

In the longitudinal analyses, 25,466 participants from 14 cohorts were included, with a median follow-up time of 5.7 years (interquartile range 3.0 to 9.5). A total of 2,423 participants developed anaemia during follow-up (14.9 per 1,000 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; Figure 2). The pooled hazard ratios for the risk of developing anaemia were 1.38 (95% CI 0.86 to 2.20) for the overt hypothyroid group, 1.18 (1.00 to 1.38) for the group with subclinical hypothyroidism, 1.15 (0.94 to 1.42) for the group with subclinical hyperthyroidism, and 1.47 (0.91 to 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 (Supplemental Table 4).

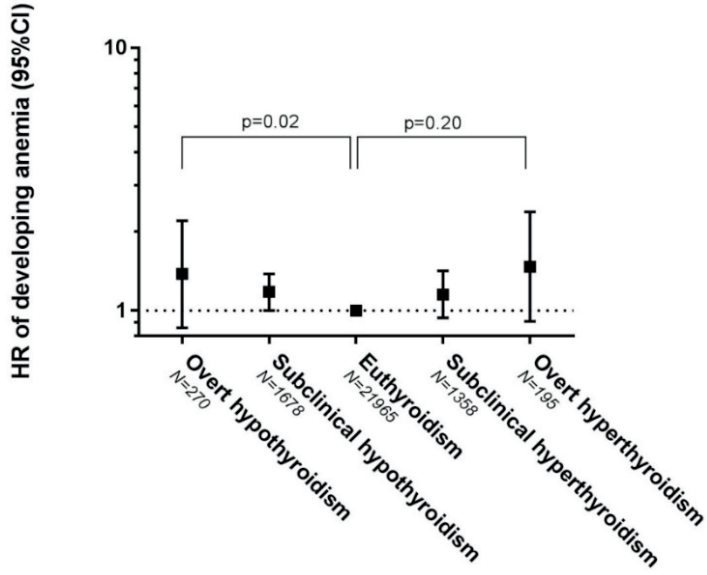


Figure 2. The pooled hazard ratios of developing anaemia during follow-up in the thyroid function groups with the 95% CI and p value for trend. Logistic regression models corrected for age and sex; reference group is euthyroidism.

Table 3. The risk of developing anaemia 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 Hypothyroidism/ Subclinical Hypothyroidism/ Subclinical Hyperthyroidism/ Overt Hyperthyroidism
All[a]	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)	270/1,678/21,965/1,358/195
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)	62/577/10,450/584/63
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)	207/1,096/11,487/773/131
Age, y						
< 50[b]	17.81 (4.06-78.24)	1.48 (0.78-2.83)	1 (ref)	1.09 (0.68-1.73)	-	16/106/3,857/343/21
50-65	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)	85/384/5,872/414/32
65-80	1.39 (0.81-2.37)[c]	1.20 (0.96-1.51)	1 (ref)	1.14 (0.83-1.57)	1.51 (0.85-2.69)	130/1,069/10,737/521/124
> 80	1.48 (0.55-4.03)[c]	1.30 (0.80-2.10)	1 (ref)	1.57 (0.98-2.50)	3.59 (0.49-26.06)	39/119/1,499/80/18
Ethnicity						
White[c]	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)	257/1,527/20,849/1,336/193
Black[d]	2.80 (0.38-20.76)	1.30 (0.59-2.83)	1 (ref)	1.57 (0.57-4.36)	-	5/41/415/16/1
Asian[e]	1.68 (0.53-5.29)	1.03 (0.70-1.51)	1 (ref)	-	-	6/109/654/6/1
Other[f]	-	-	1 (ref)	-	-	0/0/12/0/0

Data are pooled hazard ratio (95% CI) unless otherwise noted. Results were obtained by logistic regression analysis, adjusted for age (if applicable) and sex.

[a] p for trend: overt hyperthyroidism to euthyroidism, p=0.02; euthyroidism to overt hyperthyroidism p=0.20

[b] Reference group is < 50 y.

[c] p value for interaction ($p < 0.05$).

[d] Reference group is white.

[e] Only data from CHS, HEALTH ABC and PREVEND.

[f] Only data from LASA, Nagasaki, PREVEND and Rotterdam.

[g] Only data from LASA, PREVEND and Rotterdam.

Additional analyses

Cross-sectionally, haemoglobin levels (as a continuous variable) were lower (mean difference between −0.06 and −0.19 g/dL) in all groups compared with participants with euthyroidism (Supplemental Table 5). Prospectively, no differences in mean annual change in haemoglobin levels were observed among the thyroid hormone status groups (Supplemental 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 ORs in line with the unrestricted results but with wider CIs (Supplemental Tables 7 and 8).

For all main analyses, I^2 statistics remained < 40% (Supplemental Tables 9 and 10), and, in combination with size and direction of effects, statistical heterogeneity was deemed low to negligible.[27]

DISCUSSION

In this individual participant data meta-analysis, we observed a cross-sectional relation between thyroid function and anaemia; higher odds of anaemia were observed in participants with both 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 anaemia during follow-up. The longitudinal association between overt and subclinical hyperthyroidism and the risk of developing anaemia did not reach statistical significance. Prospectively, no differences in mean annual change in haemoglobin levels were observed among the thyroid hormone status groups.

The findings in the current individual participant data meta-analysis build on findings from earlier studies in which thyroid dysfunction was associated with abnormal red blood cell indices.[11-13] In this study, thyroid dysfunction, whether overt or subclinical hypothyroidism and hypothyroidism, was associated with slightly lower haemoglobin levels. Given the small difference in haemoglobin levels among thyroid function groups, the contribution of thyroid dysfunction on low haemoglobin levels or anaemia may be small. It remains to be assessed in a randomised controlled trial whether treatment of (subclinical) hypothyroidism is effective in reducing anaemia to further decide whether the findings are thought to be clinically relevant and whether these should influence practice and policies. Christ-Crain *et al.* [28] showed that erythropoietin levels increased after thyroxin treatment in patients with subclinical hypothyroidism. 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 anaemia that can be classified according to whether the anaemia 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 anaemic state. However, for subclinical and overt hyperthyroidism, several pathways have been proposed. Hyperthyroidism might be associated with anaemia via reduced erythrocyte survival due to altered iron metabolism and utilization, enhanced oxidative stress, and increased haemolysis.[29,30] 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 anaemia via deficits in the production of healthy erythrocytes, although the underlying mechanisms by which thyroid hormones and TSH may lead to anaemia are not fully understood.[31] T3, T4, and TSH may play a direct role in erythropoiesis.[32] For instance, both T3 and T4 are involved in the regulation of haematopoiesis by influencing erythroid precursor proliferative capacity.[33] In addition, a direct β2-adrenergic receptor–mediated stimulation of red cell precursors by T4 has been shown.[34] T4 has also been found to stimulate the initiation and completion of haemoglobin 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.[35] Furthermore, there is evidence that thyroid hormones affect iron transport and utilization. TSH could affect haematopoiesis by binding to a functional TSH receptor, which can be found in erythrocytes and some extrathyroidal tissues.[10] Another explanation for the co-occurrence of low thyroid function and anaemia is that there are common causes for abnormal thyroid status and anaemia. 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 anaemia, was also found to decrease the activity of thyroid peroxidase, an iron-containing enzyme involved in the synthesis of thyroid hormones.[36]

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 anaemia, standardise these definitions, and perform several standardised 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 Hill in 1965 [37] can be used as a checklist. 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. Because 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 are 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 (haemoglobin) were available. Therefore, our pooled analysis of observational studies satisfies multiple criteria of Hill. However, it remains to be assessed in a well-designed, randomised controlled trial with a considerable number of participants with (subclinical) hypothyroidism if treatment is effective in reducing anaemia. Further analysis of the data from two well-designed, randomised controlled trials for subclinical hypothyroidism in older persons (TRUST and IEMO Thyroid Trial [38,39]) could be a first attempt at uncovering the clinical relevance of thyroid influences on haemoglobin 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 normalise in one-third of cases,[40] 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 patients with euthyroidism based on 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 anaemia 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;[41] so, too, is evidence to the contrary.[42-44] 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 anaemia, but this only excluded diseases associated with inflammation. Particularly in the group of participants with subclinical hypothyroidism, the possibility of the presence of nonthyroidal 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 anaemia (cancer, chronic kidney disease, leukaemia, gastric ulcers, arthritis, or chronic obstructive pulmonary disease), menopausal state, nonthyroidal illness, concomitant medications, and iron or vitamin supplements, was not available for most cohorts.

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

REFERENCES

1. Beghe C, Wilson A, Ershler WB. Prevalence and outcomes of anemia in geriatrics: a systematic review of the literature. *Am J Med.* 2004;116 Suppl 7A(7):3S-10S.
2. Cooper DS, Biondi B. Subclinical thyroid disease. *Lancet (London, England).* 2012;379(9821):1142-1154.
3. Gaskell H, Derry S, Andrew Moore R, McQuay HJ. Prevalence of anaemia in older persons: systematic review. *BMC Geriatr.* 2008;8:1.
4. Rodondi N, den Elzen WP, Bauer DC, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA.* 2010;304(12):1365-1374.
5. Fein HG, Rivlin RS. Anemia in thyroid diseases. *The Medical clinics of North America.* 1975;59(5):1133-1145.
6. Evans ES, Rosenberg LL, Simpson ME. Erythropoietic response to calorigenic hormones. *Endocrinology.* 1961;68(3):517-532.
7. Horsley V. The Brown Lectures on Pathology. *Br Med J.* 1885;1(1261):419-423.
8. Kendrick TS, Payne CJ, Epis MR, et al. Erythroid defects in TRalpha-/- mice. *Blood.* 2008;111(6):3245-3248.
9. Das KC, Mukherjee M, Sarkar TK, Dash RJ, Rastogi GK. Erythropoiesis and erythropoietin in hypo- and hyperthyroidism. *J Clin Endocrinol Metab.* 1975;40(2):211-220.
10. Kawa MP, Grymula K, Paczkowska E, et al. Clinical relevance of thyroid dysfunction in human haematopoiesis: biochemical and molecular studies. *European journal of endocrinology / European Federation of Endocrine Societies.* 2010;162(2):295-305.
11. den Elzen WP, de Craen AJ, Mooijaart SP, Gussekloo J. Low thyroid function and anemia in old age: the Leiden 85-plus study. *J Am Geriatr Soc.* 2015;63(2):407-409.
12. Horton L, Coburn RJ, England JM, Himsworth RL. The haematology of hypothyroidism. *The Quarterly journal of medicine.* 1976;45(177):101-123.
13. Bremner AP, Feddema P, Joske DJ, et al. Significant association between thyroid hormones and erythrocyte indices in euthyroid subjects. *Clin Endocrinol (Oxf).* 2012;76(2):304-311.
14. Floriani C, Feller M, Aubert CE, et al. Thyroid Dysfunction and Anemia: A Prospective Cohort Study and a Systematic Review. *Thyroid.* 2018;28(5):575-582.
15. Tudhope GR, Wilson GM. Anaemia in hypothyroidism. Incidence, pathogenesis, and response to treatment. *The Quarterly journal of medicine.* 1960;29:513-537.
16. Vitale G, Fatti LM, Prolo S, et al. Screening for hypothyroidism in older hospitalized patients with anemia: a new insight into an old disease. *J Am Geriatr Soc.* 2010;58(9):1825-1827.
17. Gianoukakis AG, Leigh MJ, Richards P, et al. Characterization of the anaemia associated with Graves' disease. *Clin Endocrinol (Oxf).* 2009;70(5):781-787.
18. Blum MR, Bauer DC, Collet TH, et al. Subclinical thyroid dysfunction and fracture risk: a meta-analysis. *JAMA.* 2015;313(20):2055-2065.
19. Huisman M, Poppelaars J, van der Horst M, et al. Cohort profile: the Longitudinal Aging Study Amsterdam. *Int J Epidemiol.* 2011;40(4):868-876.
20. Ittermann T, Haring R, Sauer S, et al. Decreased serum TSH levels are not associated with mortality in the adult northeast German population. *European journal of endocrinology / European Federation of Endocrine Societies.* 2010;162(3):579-585.
21. Meuwese CL, van Diepen M, Cappola AR, et al. Low thyroid function is not associated with an accelerated deterioration in renal function. *Nephrol Dial Transplant.* 2019;34(4):650-659.

22. Nutritional anaemias. Report of a WHO scientific group. *World Health Organization technical report series.* 1968;405:5-37.
23. Ankle Brachial Index C, Fowkes FG, Murray GD, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA.* 2008;300(2):197-208.
24. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7(3):177-188.
25. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ.* 2010;340(feb05 1):c221.
26. Simmonds MC, Higgins JP, Stewart LA, Tierney JF, Clarke MJ, Thompson SG. Meta-analysis of individual patient data from randomized trials: a review of methods used in practice. *Clin Trials.* 2005;2(3):209-217.
27. Cochrane Handbook for Systematic Reviews of Interventions. In: www.handbook.cochrane.org.
28. Christ-Crain M, Meier C, Huber P, Zulewski H, Staub JJ, Muller B. Effect of restoration of euthyroidism on peripheral blood cells and erythropoietin in women with subclinical hypothyroidism. *Hormones (Athens, Greece).* 2003;2(4):237-242.
29. Asl SZ, Brojeni NK, Ghasemi A, Faraji F, Hedayati M, Azizi F. Alterations in osmotic fragility of the red blood cells in hypo- and hyperthyroid patients. *J Endocrinol Invest.* 2009;32(1):28-32.
30. Yucel R, Ozdemir S, Dariyerli N, Toplan S, Akyolcu MC, Yigit G. Erythrocyte osmotic fragility and lipid peroxidation in experimental hyperthyroidism. *Endocrine.* 2009;36(3):498-502.
31. Maggio M, De Vita F, Fisichella A, et al. The Role of the Multiple Hormonal Dysregulation in the Onset of "Anemia of Aging": Focus on Testosterone, IGF-1, and Thyroid Hormones. *Int J Endocrinol.* 2015;2015:292574.
32. Perrin MC, Blanchet JP, Mouchiroud G. Modulation of human and mouse erythropoiesis by thyroid hormone and retinoic acid: evidence for specific effects at different steps of the erythroid pathway. *Hematol Cell Ther.* 1997;39(1):19-26.
33. Golde DW, Bersch N, Chopra IJ, Cline MJ. Thyroid hormones stimulate erythropoiesis in vitro. *Br J Haematol.* 1977;37(2):173-177.
34. Sullivan PS, McDonald TP. Thyroxine suppresses thrombocytopoiesis and stimulates erythropoiesis in mice. *Proceedings of the Society for Experimental Biology and Medicine Society for Experimental Biology and Medicine (New York, NY).* 1992;201(3):271-277.
35. Fandrey J, Frede S, Jelkmann W. Role of hydrogen peroxide in hypoxia-induced erythropoietin production. *Biochem J.* 1994;303 (Pt 2)(Pt 2):507-510.
36. Khatiwada S, Gelal B, Baral N, Lamsal M. Association between iron status and thyroid function in Nepalese children. *Thyroid Res.* 2016;9:2.
37. Hill AB. The Environment and Disease: Association or Causation? *Proc R Soc Med.* 1965;58(5):295-300.
38. IEMO 80-plus Thyroid Trial: Nederlands Trial Register. www.trialregister.nl/trialreg/admin/rctview.asp?TC=3851. Accessed 30 July 2018.
39. Stott DJ, Rodondi N, Kearney PM, et al. Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism. *The New England journal of medicine.* 2017;376(26):2534-2544.
40. Diez JJ, Iglesias P, Burman KD. Spontaneous normalization of thyrotropin concentrations in patients with subclinical hypothyroidism. *J Clin Endocrinol Metab.* 2005;90(7):4124-4127.
41. Surks MI, Boucai L. Age- and race-based serum thyrotropin reference limits. *J Clin Endocrinol Metab.* 2010;95(2):496-502.
42. Fatourechi V. Upper limit of normal serum thyroid-stimulating hormone: a moving and now an aging target? *J Clin Endocrinol Metab.* 2007;92(12):4560-4562.

43. Kahapola-Arachchige KM, Hadlow N, Wardrop R, Lim EM, Walsh JP. Age-specific TSH reference ranges have minimal impact on the diagnosis of thyroid dysfunction. *Clin Endocrinol (Oxf)*. 2012;77(5):773-779.
44. Laurberg P, Andersen S, Carle A, Karmisholt J, Knudsen N, Pedersen IB. The TSH upper reference limit: where are we at? *Nat Rev Endocrinol*. 2011;7(4):232-239.

Supplemental table 1. Cohort specific cut-off values of free T4 and the total number of participants per thyroid category per study (baseline/follow-up).

Study	Free T4	Overt hypothyroidism	Subclinical hypothyroidism	Euthyroidism	Subclinical hyperthyroidism	Overt hyperthyroidism
Total		459/270	2,930/1,678	36,081/21,965	2,386/1,358	306/195
Bari study	0.7 – 1.8 ng/dL	-	40/19	289/183	7/4	1/0
BELFRAIL	0.9 – 1.8 ng/dL	11/8	4/3	455/286	54/34	-
Busselton Health study	9.0 – 23.0 pmol/L	13/8	97/50	1,898/1,155	52/27	14/5
Cardiovascular Health study	0.7 – 1.7 ng/dL	38/29	503/351	2,519/1,906	44/27	2/1
EPIC-Norfolk study	9.0 – 20 pmol/L	217/115	731/414	11,888/6,874	367/219	83/35
Health, Aging, and Body Composition study	0.8 – 1.8 ng/dL	23/11	313/167	2,110/1,013	79/42	6/3
InChianti study	0.8 – 2.2 ng/dL	9/6	32/24	1,054/849	88/57	17/8
Longitudinal Aging Study Amsterdam (LASA)	11 – 22 pmol/L	9/4	15/6	695/302	42/15	5/2
Leiden 85-plus Study	13 – 23 pmol/L	40/26	35/26	455/330	23/13	2/2
Nagasaki Adult Health study	0.8 – 2.5 ng/dL	13/6	143/109	800/631	8/6	1/1
Pisa cohort	7.1 – 18.5 pg/mL	3/NA	117/NA	2,025/NA	107/NA	7/NA
PREVEND study	9.14 – 23.81 mmol/L	3/3	60/49	835/698	35/28	1/1
PROSPER study	12 – 18 pmol/L	31/30	445/386	5,056/4,506	132/118	105/98
Rotterdam Study	11 – 25 pmol/L	20/12	108/64	1,577/1,102	118/71	12/6
SHIP	8.3 – 18.9 pmol/L	17/12	15/10	3,097/2,130	1,035/697	50/33
Whickham Survey	3.6 – 13.6 pmol/L	12/NA	272/NA	1,328/NA	195/NA	-

SI unit free T4 is pmol/L. Conversion factor for ng/dL is 12.87, pg/mL is 1.29, mmol/L is 1x10^9. Molecular mass for thyroxine is 776.87 g/mol

Supplemental table 2. Baseline characteristics of individuals in included studies per thyroid category per study (N=42,162).

Characteristics	Overt Hypothyroidism	Subclinical hypothyroidism	Euthyroidism	Subclinical hyperthyroidism	Overt Hyperthyroidism
Age, Median (Range), y	26-89	18-95	14-103	16-100	24-90
Bari study	-	70 (62-77)	65 (57-74)	62 (57-82)	64
BELFRAIL	84 (83-87)	85 (83-87)	84 (80-100)	84 (80-97)	-
Busselton Health study	61 (26-71)	58 (19-79)	51 (17-90)	51 (21-84)	59 (33-82)
Cardiovascular Health study	72 (65-84)	72 (65-95)	71 (64-100)	73 (65-98)	73 (68-78)
EPIC-Norfolk study	60 (41-78)	61 (40-78)	58 (40-78)	61 (40-77)	64 (42-77)
Health, Aging, and Body Composition study	73 (70-78)	75 (70-81)	74 (70-81)	76 (70-81)	74 (71-79)
InChianti study	74 (63-87)	76 (39-92)	71 (21-103)	73 (25-100)	70 (24-90)
Longitudinal Aging Study Amsterdam (LASA)	69 (59-79)	68 (56-85)	68 (55-85)	72 (58-85)	68 (63-85)
Leiden 85-plus Study	85	85	85	85	85
Nagasaki Adult Health study	65 (55-89)	58 (39-90)	57 (38-92)	54 (46-80)	83
Pisa cohort	77 (64-78)	71 (22-93)	68 (14-96)	69 (16-93)	70 (24-84)
PREVEND study	60 (56-65)	64 (36-82)	59 (35-82)	67 (45-81)	70
PROSPER study	76 (71-83)	75 (70-83)	75 (69-83)	76 (70-83)	75 (70-83)
Rotterdam Study	70 (55-81)	70 (56-86)	68 (55-93)	69 (55-89)	71 (57-82)
SHIP	56 (26-77)	52 (32-72)	47 (20-81)	57 (20-81)	62 (25-80)
Whickham Survey	55 (38-68)	52 (18-92)	45 (18-89)	43 (19-93)	-
Women (%)	337 (73.4)	1,901 (64.9)	18,535 (51.1)	1,331 (55.8)	204 (66.7)
Bari study	-	11 (27.5)	64 (22.1)	3 (42.9)	0
BELFRAIL	10 (57.9)	2 (50.0)	275 (60.4)	44 (81.5)	-
Busselton Health study	9 (69.2)	67 (69.1)	917 (48.3)	25 (48.1)	12 (85.7)
Cardiovascular Health study	24 (63.2)	327 (65.0)	1,484 (58.9)	28 (63.6)	1 (50.0)
EPIC-Norfolk study	160 (73.7)	515 (70.5)	6,314 (53.1)	233 (63.5)	54 (65.1)

Supplemental table 2. Baseline characteristics of individuals in included studies per thyroid category per study (N=42,162). (*continued*)

Characteristics	Overt Hypothyroidism	Subclinical hypothyroidism	Euthyroidism	Subclinical hyperthyroidism	Overt Hyperthyroidism
Health, Aging, and Body Composition study	16 (69.6)	172 (55.0)	1,057 (50.1)	55 (69.6)	5 (83.3)
InChianti study	7 (77.8)	21 (65.6)	582 (55.2)	53 (60.2)	12 (70.6)
Longitudinal Aging Study Amsterdam (LASA)	7 (77.8)	13 (86.7)	342 (49.2)	26 (61.9)	5 (100.0)
Leiden 85-plus Study	31 (77.5)	28 (80.0)	293 (64.4)	15 (65.2)	1 (50.0)
Nagasaki Adult Health study	10 (76.9)	88 (61.5)	478 (59.8)	2 (25.0)	0
Pisa cohort	2 (66.7)	54 (46.2)	681 (33.6)	45 (42.1)	3 (42.9)
PREVEND study	1 (33.3)	36 (60.0)	343 (41.1)	17 (48.6)	0
PROSPER study	21 (67.7)	290 (65.2)	2,498 (49.4)	92 (69.7)	82 (78.1)
Rotterdam Study	16 (80.0)	88 (81.5)	939 (59.5)	82 (69.5)	10 (83.3)
SHIP	14 (82.4)	10 (66.7)	1,573 (50.8)	523 (50.5)	19 (38.0)
Whickham Survey	9 (75.0)	179 (65.8)	695 (52.3)	88 (45.1)	-

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

Supplemental table 3. Overview of the number of participants who had anaemia at baseline or developed anaemia during follow-up per study.

Study	Overt hypothyroidism		Subclinical hypothyroidism		Euthyroidism		Subclinical hyperthyroidism		Overt hyperthyroidism	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Total cases	73 (15.9)	33 (7.2)	341 (11.6)	202 (6.9)	3,501 (9.7)	2,026 (5.6)	325 (13.6)	145 (6.1)	34 (11.1)	17 (5.6)
Bari study	-	-	11 (27.5)	4 (10.0)	56 (19.4)	25 (8.7)	2 (28.6)	1 (14.3)	0	-
BELFRAIL	0	1 (9.1)	1 (25.0)	0	94 (20.7)	44 (9.7)	11 (20.4)	7 (13.0)	-	-
Busselton Health study	2 (15.4)	2 (15.4)	6 (6.2)	2 (2.1)	62 (3.3)	48 (2.5)	5 (9.6)	2 (3.8)	1 (7.1)	0
Cardiovascular Health study	4 (10.5)	4 (10.5)	65 (12.9)	46 (9.1)	188 (7.5)	266 (10.6)	1 (2.3)	5 (11.4)	1 (50.0)	0
EPIC-Norfolk study	30 (13.8)	4 (1.8)	68 (9.3)	34 (4.7)	946 (8.0)	449 (3.8)	33 (9.0)	8 (2.2)	13 (15.7)	4 (4.8)
Health, Aging, and Body Composition study	3 (13.0)	1 (4.3)	47 (15.0)	29 (9.3)	325 (15.4)	157 (7.4)	9 (11.4)	7 (8.9)	0	1 (16.7)
InChianti study	2 (22.2)	1 (11.1)	4 (12.5)	10 (31.3)	93 (8.8)	147 (13.9)	17 (19.3)	18 (20.5)	4 (23.5)	1 (5.9)
Longitudinal Aging Study Amsterdam (LASA)	3 (33.3)	0	1 (6.7)	0	37 (5.3)	26 (3.7)	2 (4.8)	2 (48)	0	0
Leiden 85-plus Study	14 (35.0)	8 (20.0)	9 (25.7)	4 (11.4)	125 (27.5)	80 (17.6)	10 (43.5)	5 (21.7)	0	1 (50.0)
Nagasaki Adult Health study	5 (38.5)	3 (23.1)	25 (17.5)	31 (21.7)	148 (18.5)	162 (20.3)	1 (12.5)	0	0	0
Pisa cohort	1 (33.3)	NA	32 (27.4)	NA	422 (20.8)	NA	33 (30.8)	NA	2 (28.6)	NA
PREVEND study	0	2 (66.7)	4 (6.7)	10 (16.7)	98 (11.7)	67 (8.0)	4 (11.4)	3 (8.6)	0	0
PROSPER study	1 (3.2)	2 (6.5)	44 (9.9)	18 (4.0)	347 (6.9)	174 (3.4)	7 (5.3)	5 (3.8)	3 (2.9)	4 (3.8)
Rotterdam Study	3 (15.0)	3 (15.0)	9 (8.3)	14 (13.0)	91 (5.8)	183 (11.6)	4 (3.4)	12 (10.2)	2 (16.7)	2 (16.7)
SHIP	4 (23.5)	2 (11.8)	4 (26.7)	0	404 (13.0)	198 (6.4)	169 (16.3)	70 (6.8)	8 (16.0)	4 (8.0)
Whickham Survey	1 (8.3)	NA	11 (4.0)	NA	65 (4.9)	NA	17 (8.7)	NA	-	NA

Abbreviations: NA, data not available.

Supplemental table 4. The risk of developing anaemia during follow-up according to thyroid hormone status at baseline.

	Overt hypothyroidism	Subclinical hypothyroidism	Euthyroidism	Subclinical hyperthyroidism	Overt hyperthyroidism
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)
Median follow-up					
< 5 years[b]	0.95 (0.60-1.50)	1.06 (0.87-1.30)	1 (ref)	1.11 (0.77-1.61)	1.43 (0.74-2.77)
≥ 5 years[c]	2.22 (1.11-4.43)	1.37 (1.02-1.85)	1 (ref)	1.21 (0.91-1.61)	1.51 (0.75-3.05)

[a] Results were obtained by cox regression analysis, adjusted for age (if applicable) and sex

[b] Cohorts: Bari study, BELFRAIL, Cardiovascular Health study, EPIC-Norfolk study, Longitudinal Aging Study Amsterdam, Leiden 85-plus Study and PROSPER study

[c] Cohorts: Busselton Health study, Health, Aging, and Body composition study, InChianti study, Nagasaki Adult Health study, PREVEND study, Rotterdam Study and SHIP

Supplemental table 5. The mean difference in haemoglobin levels (continuous in g/dL) at baseline compared to euthyroidism depending on thyroid status.

	Overt hypothyroidism		Subclinical hypothyroidism		Euthyroidism		Subclinical hyperthyroidism		Overt hyperthyroidism	
	n	Mean diff. (95% CI)	n	Mean diff. (95% CI)	n	Mean diff. (95% CI)	n	Mean diff. (95% CI)	n	Mean diff. (95% CI)
All	459	-0.19 (-0.32- -0.06)	2,930	-0.07 (-0.13- -0.01)	36,081	(ref).	2,386	-0.06 (-0.13-0.01)	309	-0.07 (-0.20-0.05)
Sex										
Male	122	-0.31 (-0.52- -0.10)	1,029	-0.08 (-0.15-0.00)	17,546	(ref).	1,055	-0.06 (-0.13-0.02)	102	0.06 (-0.16-0.28)
Female	337	-0.18 (-0.34- -0.02)	1,901	-0.08 (-0.14- -0.02)	18,535	(ref).	1,331	-0.09 (-0.22-0.04)	204	-0.14 (-0.29-0.01)
Age										
< 50 years	47	-0.23 (-0.55-0.09)	308	-0.13 (-0.28-0.02)	6,902	(ref).	599	-0.01 (-0.09-0.08)	30	-0.01 (-0.64-0.62)
50-65 years	132	-0.24 (-0.42- -0.06)	677	-0.05 (-0.14-0.04)	9,715	(ref).	672	-0.12 (-0.25-0.01)	98	-0.06 (-0.26-0.15)
65-80 years	215	-0.21 (-0.45-0.03)	1,711	-0.10 (-0.17- -0.02)	16,814	(ref).	948	0.01 (-0.15-0.18)	186	-0.09 (-0.28-0.09)
> 80 years	65	-0.20 (-0.53-0.12)	234	0.01 (-0.18-0.21)	2,646	(ref).	168	-0.24 (-0.45- -0.03)	27	0.29 (-0.15-0.73)
Ethnicity										
White	431	-0.18 (-0.32- -0.05)	2,687	-0.09 (-0.16- -0.01)	34,154	(ref).	2,339	-0.06 (-0.13-0.01)	303	-0.08 (-0.21-0.04)
Black[b]	12	-0.19 (-0.88-0.50)	98	-0.20 (-0.45-0.05)	1,007	(ref).	35	0.11 (-0.31-0.52)	2	0.72 (-0.98-2.41)
Asian[c]	13	-0.53 (-1.22-0.16)	143	0.00 (-0.23-0.22)	800	(ref).	8	-0.68 (-1.55-0.19)	1	0.37 (-2.08-2.83)
Other[d]	-	-	-	-	13	(ref).	1	1.48 (-0.66-3.62)	-	-
Without medication	201	-0.15 (-0.32-0.01)	1,848	-0.08 (-0.17-0.01)	20,451	(ref).	1,625	-0.05 (-0.14-0.05)	138	0.08 (-0.10-0.26)

[a] Results were obtained by linear 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

Supplemental table 6. The mean difference in annual change in haemoglobin levels (continuous in g/dL) compared to euthyroidism depending on thyroid hormone status at baseline.

	Overt hypothyroidism		Subclinical hypothyroidism		Euthyroidism		Subclinical hyperthyroidism		Overt hyperthyroidism	
	n	Mean diff. (95% CI)	n	Mean diff. (95% CI)	n	Mean diff. (95% CI)	n	Mean diff. (95% CI)	n	Mean diff. (95% CI)
All	459	-0.19 (-0.32- -0.06)	2,930	-0.07 (-0.13- -0.01)	36,081	(ref).	2,386	-0.06 (-0.13-0.01)	309	-0.07 (-0.20-0.05)
Sex										
Male	122	-0.31 (-0.52- -0.10)	1,029	-0.08 (-0.15-0.00)	17,546	(ref).	1,055	-0.06 (-0.13-0.02)	102	0.06 (-0.16-0.28)
Female	337	-0.18 (-0.34- -0.02)	1,901	-0.08 (-0.14- -0.02)	18,535	(ref).	1,331	-0.09 (-0.22-0.04)	204	-0.14 (-0.29-0.01)
Age										
< 50 years	47	-0.23 (-0.55-0.09)	308	-0.13 (-0.28-0.02)	6,902	(ref).	599	-0.01 (-0.09-0.08)	30	-0.01 (-0.64-0.62)
50-65 years	132	-0.24 (-0.42- -0.06)	677	-0.05 (-0.14-0.04)	9,715	(ref).	672	-0.12 (-0.25-0.01)	98	-0.06 (-0.26-0.15)
65-80 years	215	-0.21 (-0.45-0.03)	1,711	-0.10 (-0.17- -0.02)	16,814	(ref).	948	0.01 (-0.15-0.18)	186	-0.09 (-0.28-0.09)
> 80 years	65	-0.20 (-0.53-0.12)	234	0.01 (-0.18-0.21)	2,646	(ref).	168	-0.24 (-0.45- -0.03)	27	0.29 (-0.15-0.73)
Ethnicity										
White	431	-0.18 (-0.32- -0.05)	2,687	-0.09 (-0.16- -0.01)	34,154	(ref).	2,339	-0.06 (-0.13-0.01)	303	-0.08 (-0.21-0.04)
Black[b]	12	-0.19 (-0.88-0.50)	98	-0.20 (-0.45-0.05)	1,007	(ref).	35	0.11 (-0.31-0.52)	2	0.72 (-0.98-2.41)
Asian[c]	13	-0.53 (-1.22-0.16)	143	0.00 (-0.23-0.22)	800	(ref).	8	-0.68 (-1.55-0.19)	1	0.37 (-2.08-2.83)
Other[d]	-	-	-	-	13	(ref).	1	1.48 (-0.66-3.62)	-	-
Without medication	201	-0.15 (-0.32-0.01)	1,848	-0.08 (-0.17-0.01)	20,451	(ref).	1,625	-0.05 (-0.14-0.05)	138	0.08 (-0.10-0.26)

[a] Results were obtained by linear 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

Supplemental table 7. Sensitivity analyses: The risk of having anaemia at baseline depending on thyroid hormone status.

		Overt hypothyroidism	Subclinical hypothyroidism	Euthyroidism	Subclinical hyperthyroidism	Overt hyperthyroidism
Pooled OR (95% CI)[a]						
Without antithyroid medication or thyroid hormone replacement therapy[b]		1.95 (1.27-3.01)	1.28 (1.06-1.54)	1 (ref.)	1.29 (0.92-1.81)	1.83 (0.64-5.26)
	N	*204*	*1,845*	*20,451*	*1,664*	*143*
Without elevated CRP levels[c]		2.54 (1.31-4.93)	0.93 (0.60-1.45)	1 (ref.)	1.31 (1.02-1.66)	1.36 (0.60-3.09)
	N	*87*	*242*	*5,547*	*684*	*55*

Excluded the following medications: levothyroxine, thiamazol, ATC codes H03AA, H03CA, H05AA, H03B, H05B and by the cohort's expertise classified as antithyroid medication or thyroid hormone replacement therapy

[a] Results were obtained by logistic regression analysis, adjusted for age (if applicable) and sex

[b] No data on thyroid medication from EPIC-Norfolk, PISA and PREVEND

[c] Analysed in studies containing CRP records: Bari, Belfrail, InChianti, LASA, Leiden 85-plus, PREVEND, Rotterdam and SHIP. CRP >20 mg/L was considered elevated.

Supplemental table 8. Sensitivity analyses: The risk developing anaemia during follow-up depending on thyroid hormone status at baseline.

		Overt hypothyroidism	Subclinical hypothyroidism	Euthyroidism	Subclinical hyperthyroidism	Overt hyperthyroidism
Pooled OR (95% CI)[a]						
Without antithyroid medication or thyroid hormone replacement therapy[b]		2.00 (0.65-6.19)	1.13 (0.86-1.48)	1 (ref)	1.58 (1.16-2.16)	2.08 (0.86-5.03)
	N	*66*	*836*	*10,792*	*292*	*64*
Without elevated CRP levels[c]		1.72 (0.81-3.68)	1.70 (1.20-2.41)	1 (ref)	1.31 (1.01-1.69)	2.14 (0.67-6.79)
	N	*57*	*168*	*3,960*	*434*	*32*

Excluded the following medications: levothyroxine, thiamazol, ATC codes H03AA, H03CA, H05AA, H03B, H05B and by the cohort's expertise classified as antithyroid medication or thyroid hormone replacement therapy

[a] Results were obtained by logistic regression analysis, adjusted for age (if applicable) and sex

[b] No data on thyroid medication from EPIC-Norfolk, PISA and PREVEND

[c] Analysed in studies containing CRP records: Bari, Belfrail, InChianti, LASA, Leiden 85-plus, PREVEND, Rotterdam and SHIP. CRP >20 mg/L was considered elevated.

Supplemental table 9. Individual cohort estimates for the cross-sectional analysis.

Thyroid status	Odds ratio	95% CI		Weight	I^2
		Lower	Upper		
Overt hypothyroidism	1.84	1.35	2.50		10%
Bari study	NA				
BELFRAIL	NA				
Busselton Health study	4.97	1.07	23.05	3.9%	
Cardiovascular Health study	1.50	0.52	4.33	7.7%	
EPIC-Norfolk study	1.62	1.09	2.40	34.4%	
Health- Aging- and Body Composition study	0.92	0.27	3.12	5.9%	
InChianti study	2.67	0.53	13.54	3.5%	
Longitudinal Aging Study Amsterdam (LASA)	14.10	3.06	64.90	3.9%	
Leiden 85-plus Study	1.63	0.81	3.28	15.7%	
Nagasaki Adult Health study	2.01	0.63	6.39	6.5%	
Pisa cohort	1.52	0.13	17.06	1.6%	
PREVEND study	NA				
PROSPER study	0.43	0.06	3.21	2.3%	
Rotterdam Study	3.12	0.88	11.10	5.5%	
SHIP	1.72	0.55	5.33	6.8%	
Whickham Survey	1.35	0.17	10.79	2.2%	
Subclinical hypothyroidism	1.21	1.02	1.43		28%
Bari study	1.37	0.64	2.95	4.0%	
BELFRAIL	1.19	0.12	11.86	0.5%	
Busselton Health study	1.72	0.59	4.99	2.2%	
Cardiovascular Health study	1.80	1.33	2.44	13.9%	
EPIC-Norfolk study	1.06	0.81	1.37	15.9%	
Health- Aging- and Body Composition study	0.98	0.70	1.37	12.7%	
InChianti study	1.02	0.34	3.05	2.1%	
Longitudinal Aging Study Amsterdam (LASA)	1.73	0.21	14.46	0.6%	
Leiden 85-plus Study	1.08	0.48	2.40	3.7%	
Nagasaki Adult Health study	0.87	0.54	1.39	8.4%	
Pisa cohort	1.38	0.90	2.11	9.5%	
PREVEND study	0.47	0.17	1.35	2.3%	
PROSPER study	1.48	1.06	2.07	12.7%	
Rotterdam Study	1.56	0.75	3.23	4.3%	
SHIP	2.20	0.69	7.00	1.9%	
Whickham Survey	0.69	0.36	1.35	5.1%	

Supplemental table 9. Individual cohort estimates for the cross-sectional analysis. (*continued*)

Thyroid status	Odds ratio	95% CI		Weight	I^2
		Lower	Upper		
Subclinical hyperthyroidism	1.27	1.03	1.57		35%
Bari study	1.71	0.31	9.42	1.4%	
BELFRAIL	1.12	0.55	2.29	6.3%	
Busselton Health study	3.13	1.20	8.17	4.0%	
Cardiovascular Health study	0.24	0.03	1.75	1.1%	
EPIC-Norfolk study	1.07	0.74	1.54	13.5%	
Health- Aging- and Body Composition study	0.72	0.36	1.47	6.4%	
InChianti study	2.01	1.11	3.64	8.2%	
Longitudinal Aging Study Amsterdam (LASA)	0.92	0.21	4.04	1.9%	
Leiden 85-plus Study	2.13	0.89	5.09	4.7%	
Nagasaki Adult Health study	0.82	0.10	6.83	1.0%	
Pisa cohort	1.63	1.06	2.51	11.7%	
PREVEND study	0.82	0.28	2.38	3.3%	
PROSPER study	0.75	0.34	1.61	5.6%	
Rotterdam Study	0.54	0.19	1.51	3.6%	
SHIP	1.24	1.01	1.51	18.8%	
Whickham Survey	2.11	1.20	3.71	8.6%	
Overt hyperthyroidism	1.69	1.00	2.87		34%
Bari study	NA				
BELFRAIL	NA				
Busselton Health study	1.95	0.25	15.41	5.6%	
Cardiovascular Health study	12.82	0.74	222.89	3.1%	
EPIC-Norfolk study	2.03	1.11	3.70	26.4%	
Health- Aging- and Body Composition study	NA				
InChianti study	3.18	0.95	10.71	12.9%	
Longitudinal Aging Study Amsterdam (LASA)	NA				
Leiden 85-plus Study	NA				
Nagasaki Adult Health study	NA				
Pisa cohort	1.66	0.30	9.14	7.8%	
PREVEND study	NA				
PROSPER study	0.40	0.12	1.26	13.7%	
Rotterdam Study	3.39	0.72	16.07	8.9%	
SHIP	1.27	0.59	2.75	21.6%	
Whickham Survey	NA				

Abbreviations: CI, Confidence interval; NA, data not available.

Supplemental table 10. Individual cohort estimates for the longitudinal analysis.

Thyroid status	Hazard ratio	95% CI		Weight	I^2
		Lower	Upper		
Overt hypothyroidism	1.38	0.86	2.20		33%
Bari study	NA				
BELFRAIL	0.96	0.13	7.02	4.7%	
Busselton Health study	4.84	1.17	20.04	8.0%	
Cardiovascular Health study	1.00	0.37	2.69	12.8%	
EPIC-Norfolk study	0.44	0.16	1.18	12.8%	
Health- Aging- and Body Composition study	0.72	0.10	5.17	4.8%	
InChianti study	0.96	0.13	6.85	4.8%	
Longitudinal Aging Study Amsterdam (LASA)	NA				
Leiden 85-plus Study	1.20	0.58	2.49	17.2%	
Nagasaki Adult Health study	1.68	0.53	5.29	10.7%	
Pisa cohort	NA				
PREVEND study	7.29	1.79	29.79	8.1%	
PROSPER study	1.81	0.45	7.33	8.2%	
Rotterdam Study	NA				
SHIP	1.42	0.35	5.75	8.1%	
Whickham Survey	NA				
Subclinical hypothyroidism	1.18	1.00	1.38		17%
Bari study	1.51	0.52	4.41	2.4%	
BELFRAIL	0.76	0.19	3.16	1.4%	
Busselton Health study	NA				
Cardiovascular Health study	0.93	0.68	1.28	19.0%	
EPIC-Norfolk study	1.19	0.84	1.69	16.3%	
Health- Aging- and Body Composition study	1.14	0.77	1.70	13.7%	
InChianti study	2.24	1.17	4.28	6.1%	
Longitudinal Aging Study Amsterdam (LASA)	NA				
Leiden 85-plus Study	0.70	0.34	1.46	4.9%	
Nagasaki Adult Health study	1.03	0.70	1.51	14.3%	
Pisa cohort	NA				
PREVEND study	2.16	1.10	4.25	5.6%	
PROSPER study	1.26	0.77	2.05	9.8%	
Rotterdam Study	1.29	0.70	2.39	6.7%	
SHIP	NA				
Whickham Survey	NA				

Supplemental table 10. Individual cohort estimates for the longitudinal analysis. (*continued*)

Thyroid status	Hazard ratio	95% CI		Weight	I^2
		Lower	Upper		
Subclinical hyperthyroidism	1.15	0.94	1.42		10%
Bari study	2.40	0.31	18.49	1.0%	
BELFRAIL	1.31	0.59	2.93	6.0%	
Busselton Health study	1.91	0.46	7.87	2.1%	
Cardiovascular Health study	1.61	0.66	3.92	5.0%	
EPIC-Norfolk study	0.52	0.26	1.05	7.8%	
Health- Aging- and Body Composition study	1.19	0.55	2.55	6.7%	
InChianti study	1.84	1.13	3.00	14.4%	
Longitudinal Aging Study Amsterdam (LASA)	1.65	0.38	7.07	1.9%	
Leiden 85-plus Study	1.44	0.58	3.56	4.9%	
Nagasaki Adult Health study	NA				
Pisa cohort	NA				
PREVEND study	1.02	0.32	3.25	3.0%	
PROSPER study	1.14	0.47	2.79	5.0%	
Rotterdam Study	1.30	0.70	2.40	9.8%	
SHIP	0.91	0.69	1.21	32.4%	
Whickham Survey	NA				
Overt hyperthyroidism	1.47	0.91	2.38		0%
Bari study	NA				
BELFRAIL	NA				
Busselton Health study	NA				
Cardiovascular Health study	NA				
EPIC-Norfolk study	1.43	0.53	3.84	23.8%	
Health- Aging- and Body Composition study	2.32	0.32	16.59	6.0%	
InChianti study	1.21	0.17	8.69	6.0%	
Longitudinal Aging Study Amsterdam (LASA)	NA				
Leiden 85-plus Study	3.59	0.49	26.06	5.9%	
Nagasaki Adult Health study	NA				
Pisa cohort	NA				
PREVEND study	NA				
PROSPER study	1.13	0.42	3.06	23.3%	
Rotterdam Study	2.91	0.72	11.76	11.8%	
SHIP	1.03	0.38	2.79	23.3%	
Whickham Survey	NA				

Abbreviations: CI, Confidence interval; NA, data not available.