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Thyroid dysfunction and anemia in a large population-based study

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Structured summary:

Objective and background

Anemia and thyroid dysfunction are common and often co-occur. Current guidelines recommend the assessment of thyroid function in the work-up of anemia, although evidence on this association is scarce.

Patients and Methods

In the "European Prospective Investigation of Cancer" (EPIC)-Norfolk population-based cohort, we **aimed to** examine the prevalence and type of anemia (defined as hemoglobin <13 g/dl for men and <12 g/dl for women) **according to different thyroid function groups**.

Results

The mean age of the 8791 participants was 59.4 (SD 9.1) years and 55.2% were women. Thyroid dysfunction was present in 437 (5.0%) and anemia in 517 (5.9%) participants. After excluding 121 participants with three most common causes of anemia (chronic kidney disease, inflammation, iron deficiency), anemia was found in 4.7% of euthyroid participants. Compared with the euthyroid group, the prevalence of anemia was significantly higher in overt hyperthyroidism (14.6%, $P < .01$), higher with borderline significance in overt hypothyroidism (7.7%, $P = .05$) and not increased in subclinical thyroid dysfunction (5.0% in subclinical hypothyroidism, 3.3% in subclinical hyperthyroidism). Anemia associated with thyroid dysfunction was mainly normocytic (94.0%), and rarely macrocytic (6.0%).

Conclusion

The prevalence of anemia was higher in overt hyperthyroidism, but not increased in subclinical thyroid dysfunction. Systematic measurement of thyroid-stimulating hormone in anemic patients is likely to be useful only after excluding common causes of anemia.

Introduction:

Anemia and thyroid dysfunction are common disorders that often co-occur in the elderly.[1,2] More than 10% of patients aged ≥65 years have anemia[3] and the prevalence of subclinical thyroid dysfunction increases with age, with 15-20% of those above 60 years having subclinical hypothyroidism.[4-5] **Hypothyroidism may lead to anemia because of bone marrow repression and decrease in erythropoietin secretion,[6] while the relationship between hyperthyroidism and anemia is less clear.[7-10]** In a recent study, the prevalence of hypothyroidism in 316 hospitalized patients above 65 years was significantly higher in the presence of anemia (31 out of 155 patients) compared to their counterparts without anemia (16 out of 161; *P* = .01);[1] however, this study was limited by its small size, by the hospital setting, and did not differentiate between overt and subclinical hypothyroidism.

Furthermore, the relationship between thyroid dysfunction and the type of anemia (micro-, normo- or macrocytic) remains unclear. Hypothyroidism has been associated with macrocytosis, and even though this association seems uncommon and particularly related to severe hypothyroidism, TSH measurement is commonly recommended in the work-up of macrocytosis.[11-14] Other studies showed that anemia due to thyroid dysfunction is more often normocytic than macrocytic.[6,15-17] Even though data on the association between thyroid dysfunction and anemia remain scarce, TSH measurement is still recommended in the initial work-up of anemia.[2,11-14]

To fill this gap in knowledge, we examined the prevalence of anemia according to different thyroid function groups and assessed the type of anemia associated with thyroid dysfunction in a large population-based study.

Methods:

Patients and laboratory data

After excluding participants with central thyroid dysfunction (normal TSH and abnormal free T4 [fT4] or concomitant high/low TSH and fT4, N=331), we examined 8791 men and women aged 39-79 years with measured thyroid function **(TSH and fT4)** and hematological parameters at baseline in the population-based "European Prospective

Investigation of Cancer" (EPIC)-Norfolk study previously detailed elsewhere.[18] The study was approved by the Norwich local research ethics committee, UK, and written informed consent was provided by all participants.

Thyroid dysfunction was defined as hypothyroidism when TSH was >4.49 mIU/l, either subclinical (SHypo) with normal fT4 or overt (OHypo) with low fT4, and as hyperthyroidism when TSH was <0.45 mIU/l, either subclinical (SHyper) with normal fT4 or overt (OHyper) with elevated fT4. Following the WHO definition,[19] anemia was defined as hemoglobin (Hb) <13 g/dl for men and <12 g/dl for women, and further classified into microcytic anemia with mean corpuscular volume (MCV) <80 fl, normocytic with MCV 80 to 100 fl, and macrocytic with MCV >100 fl. Ferritin, C-reactive protein (CRP) and creatinine were measured at baseline to assess three most common causes of anemia.[20-21] For this purpose, iron deficiency was defined as ferritin <15 ng/ml,[22] inflammatory disease as CRP ≥10 mg/l[23] and chronic kidney disease as estimated glomerular filtration rate (eGFR) ≤30 ml/min/1.73m^2, using the MDRD equation,[24-25] while less conservative cut-offs were used in sensitivity analyses. [22,26] In the EPIC-Norfolk study, 8791 adults had TSH, ferritin, CRP and eGFR measurements and were available for this analysis.

Statistical analyses

We studied the prevalence of anemia in the overall sample and in five groups defined according to their thyroid status (euthyroid, OHypo, SHypo, SHyper, OHyper). We compared the prevalence of anemia between these groups using Fisher's exact tests of association. We compared Hb concentration across the groups using age and sex adjusted quadratic pattern linear regression with robust standard errors.

Results and Discussion

Among the 8791 participants, the mean age was 59.4 (SD 9.1) years and 55.2% were women. Thyroid dysfunction was present in **917 (10.4%)** participants and anemia in 517 (5.9%). Among the anemic participants, 56 (10.8%) had iron deficiency, 58 (11.2%) an inflammatory state, 6 (1.2%) chronic kidney disease, and 1 (0.2%) an inflammatory state and chronic kidney disease. After excluding participants with these three most common causes of

anemia, the prevalence of thyroid dysfunction (abnormal TSH) was 12.6% (50 out of 396 participants). The prevalence of anemia was 4.5% among participants with euthyroidism compared to 7.7% in participants with OHypo (*P* = .05), 5.0% in those with SHypo (*P* = .57), 3.3% in those with SHyper (*P* = .50) and 14.6% in those with OHyper (*P* < .01, Table 1). Only 4.8% (19/396) of these anemic participants had overt thyroid dysfunction. In a sensitivity analysis using less conservative cut-offs, 289 of the 517 anemic participants had chronic kidney disease with eGFR <60 ml/min/1.73m^2,[26] iron deficiency with ferritin <30 ng/ml,[22] and/or inflammatory disease. After excluding these participants, the proportion of 4.8% with anemia and overt thyroid dysfunction dropped to 3.1% (7/228, data not shown). **In another sensitivity analysis with lower Hb cut-offs (<12 g/dl for men and <11 g/dl for women), the prevalence of anemia was 3.0% (263 out of 8699) and remained significantly higher in participants with OHyper only, compared to euthyroidism (10.4% versus 2.9%, *P* < .01).** Anemia was normocytic in 94.0% and macrocytic in 6.0% of the participants with thyroid dysfunction, but never microcytic (Table 2).

In age and sex adjusted analyses, Hb concentration was lower in participants with both hyper- or hypothyroid dysfunction compared to the euthyroid state (*P*-value for quadratic pattern < .001). The only group which significantly differed from the euthyroid reference was OHyper (Hb -0.49 g/dl; CI -0.93 to -0.05; *P* = .03), while the difference was borderline significant for OHypo (Hb -0.17 g/dl; CI -0.33 to -0.00; *P* = .05; Figure 1).

In this large population-based cohort, the prevalence of anemia was higher among adults with overt hyperthyroidism, borderline significantly higher in those with overt hypothyroidism, while it did not differ in those with subclinical thyroid dysfunction, compared to the euthyroid state. Although most guidelines recommend a systematic TSH measurement among patients with anemia,[2,11-14] screening for thyroid dysfunction leads to the identification of only 4.8% (19/396) of adults with overt thyroid dysfunction after excluding three other common causes of anemia. This proportion might have been even further reduced by excluding participants with anemia due to vitamin B12 and/or folate deficiency, which were not assessed in the EPIC-Norfolk cohort and account for about 14% of causes of mainly macrocytic anemia in

other population-based studies.[20] A previous small study (n = 400) in ambulatory care found that the prevalence of anemia, after excluding other common etiologies, was significantly higher in patients with overt (43%, *P* = .0003) or subclinical (39%, *P* = .021) hypothyroidism when compared with healthy controls (23%).[6] Our results suggest a higher prevalence of anemia in participants with overt, but not in those with subclinical hypothyroidism. This partial discrepancy could be explained by the high prevalence of anemia (33% compared to ours at 5.9%), possibly due to different population characteristics and study design; this previous study was indeed not population-based and included 60-70% participants with anemia of chronic disease.[6]

We found a high prevalence of anemia in participants with hyperthyroidism (14.6%). Data on this association are very scarce, mainly consisting of case reports.[7-8] Several mechanisms have been proposed for this association, such as anti-thyroid drugs toxicity leading to aplasia, auto-immune hemolysis, impairment in the utilization of iron or increased oxidative stress leading to increased erythrocyte osmotic fragility and hemolysis.[7-10] Further studies should confirm this finding.

The small prevalence of macrocytosis in our study is consistent with previous studies[10-13] and further supports the fact that macrocytosis, although traditionally associated with hypothyroidism, is probably a rare finding in this population and rather relates to severe hypothyroidism.[11-14] However, studies with larger number of participants with macrocytosis are warranted to confirm our findings.

Our study has some limitations. TSH was measured only once at baseline, which is a limitation of most previous cohorts on the risks associated with thyroid dysfunction[27-29] and we might have found a stronger relationship between subclinical thyroid dysfunction and anemia if we had studied only participants with persistent subclinical thyroid dysfunction. We did not measure vitamin B12 and folate; however, daily folate and vitamin B12 intakes were 200-350 µg[30] and 2-14 µg[31] respectively in the EPIC-Norfolk cohort, which fulfils the current nutritional recommendations for both vitamins.[31-32]

In conclusion, our data from the largest population-based study on this issue suggest that **the prevalence of anemia is higher in overt hyperthyroidism and borderline statistically significant higher in overt hypothyroidism, but not increased in subclinical thyroid dysfunction.** TSH measurement should not be routinely recommended in the initial work-up of anemia, but only after excluding other common causes, such as iron deficiency, chronic kidney disease, inflammatory disease, **vitamin B12 and folate deficiency**. Furthermore, if measured in the etiologic work-up of anemia, TSH should not be restricted to the macrocytic cases.

Authors Contributions: Prof Rodondi had full access to all of the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis and is the guarantor. *Study concept and design:* Rodondi. *Acquisition of data:* Luben and Khaw. *Analysis and interpretation of data:* M'Rabet-Bensalah, Aubert, Coslovsky and Rodondi. *Drafting of the manuscript:* M'Rabet-Bensalah, Aubert Rodondi. *Critical revision of the manuscript for important intellectual content:* den Elzen, Aujesky, Luben, Khaw, Coslovsky, Collet, Baumgartner, Angelillo-Scherrer. *Statistical analysis:* Coslovsky. *Study supervision:* Rodondi.

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Figure legend:

Figure 1. Comparison of hemoglobin (Hb) levels with 95% confidence intervals (CI) across thyroid function groups, adjusted for age and sex. Quadratic pattern linear analysis showed that participants in the euthyroid state had the highest levels of Hb, and that Hb values were lower in the participants with both hyper- or hypothyroid dysfunction, with a greater difference in the participants with overt than subclinical thyroid dysfunction (*P*-value for quadratic pattern < .001). The only group which significantly differed from the euthyroid reference group was OHyper (Hb -0.49 g/dl; CI -0.93 to -0.05; *P* = .03), while the difference was borderline significant for OHypo (Hb -0.17 g/dl; CI -0.33 to -0.00; *P* = .05).

Abbreviations: OHypo: overt hypothyroidism; SHypo: subclinical hypothyroidism; SHyper: subclinical hyperthyroidism; OHyper: overt hyperthyroidism.

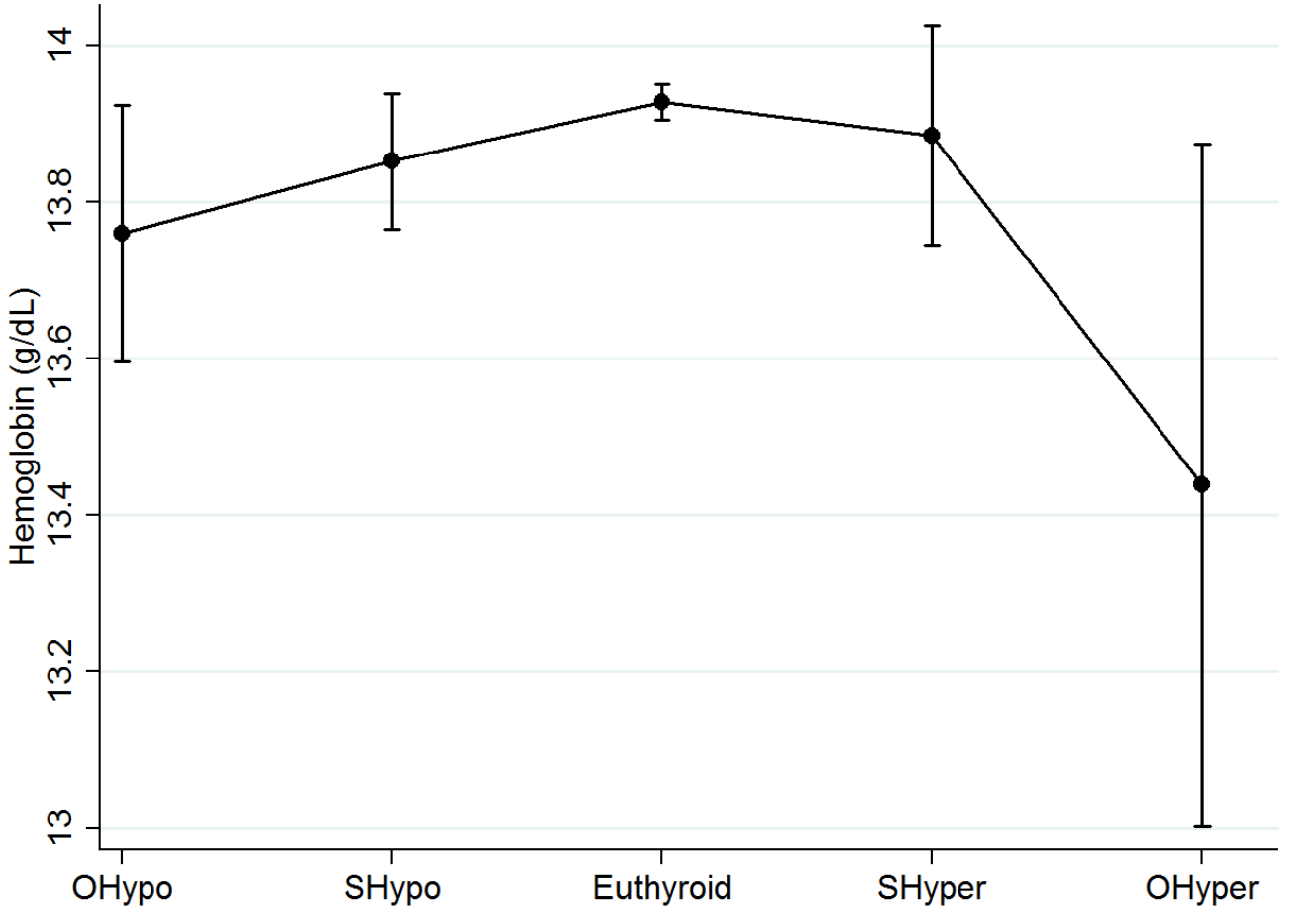

Table 1. Prevalence of anemia within the different thyroid function groups after excluding the participants with three most common causes of anemia.*

Thyroid function group	**Total**	**Anemia**	***P*-value** §
	n = 8670	n = 396 (4.5%)	
Overt hypothyroidism	143	12 (7.7)	.05
Subclinical hypothyroidism	461	24 (5.0)	.57
Euthyroidism (reference)	7424	346 (4.5)	-
Subclinical hyperthyroidism	205	7 (3.3)	.50
Overt hyperthyroidism	41	7 (14.6)	< .01

* 121 participants were excluded as they had iron deficiency (defined as ferritin <15 ng/ml, n = 56), inflammatory state (CRP ≥10 mg/l, n = 58), chronic kidney disease (estimated glomerular filtration rate ≤30 ml/min/1.73m^2, n = 6), or both inflammatory state and chronic kidney disease (n = 1). In a sensitivity analysis using less conservative cut-offs for chronic kidney disease (eGFR <60 ml/min/1.73m^2),[22] and iron deficiency (ferritin <30 ng/ml),[18] 289/517 participants had at least one of these three common causes.

§ *P*-value for the significance of the difference of prevalence of anemia in each thyroid function group compared to the euthyroid state (reference group).

Table 2. Distribution of mean corpuscular volume (MCV) within the different thyroid function groups in the participants with anemia after the exclusion of three most common causes of anemia (n = 396).*

Thyroid function group	**MCV <80 fl**	**MCV 80-100 fl**	**MCV >100 fl**
	n = 10 (2.5%)	n = 376 (95.0%)	n = 10 (2.5%)
Overt and subclinical hypothyroidism	0 (0.0)	34 (94.4)	2 (5.6) §
Euthyroidism	10 (2.9)	329 (95.1)	7 (2.0)
Overt and subclinical hyperthyroidism	0 (0.0)	13 (92.9)	1 (7.1) §
Fisher's exact test° = .28			

***** defined as ferritin <15 ng/ml, CRP ≥10 mg/l and/or estimated glomerular filtration rate (eGFR) ≤30 ml/min/1.73m^2.

§ 1 participant with subclinical hypothyroidism, 1 participant with overt hypothyroidism and 1 participant with subclinical hyperthyroidism.

° Fisher's exact test for difference in MCV category (<80 fl, 80-100 fl, >100 fl) across the three different thyroid function groups (overt and subclinical hypothyroidism; euthyroidism; overt and subclinical hyperthyroidism).