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Prevalence of Undiagnosed Hypothyroidism in Europe: A Systematic Review and Meta-Analysis

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Keywords
Undiagnosed hypothyroidism · Subclinical hypothyroidism · Prevalence · Systematic review · Meta-analysis

Abstract
Background: Patients with undiagnosed hypothyroidism are not treated for the disease and are at high risk of developing serious complications, with major impact on public health. There is a need to systematically review the available evidence on this topic. ***Objective:*** To identify the prevalence of undiagnosed hypothyroidism in Europe. ***Methods:*** A systematic review of the literature (Medline, EMBASE, and Cochrane Central) was performed to identify epidemiological studies on the prevalence of undiagnosed hypothyroidism among European populations published between January 2008 and April 2018. The Newcastle-Ottawa Scale was used to assess the methodological quality of the included studies. Random-effects meta-analyses were performed to pool estimates of proportions (with 95% confidence intervals [CIs]) of undiagnosed (1) subclinical, (2) overt, and (3) total hypothyroidism. ***Results:*** The search returned 15,565 citations (4,526 duplicates). Twenty papers were included in the study. Fourteen and 6 studies were of good and moderate methodological quality, respectively. The results of the meta-analyses were as follows for the prevalence of undiagnosed hypothyroidism: subclinical, 4.11% (95% CI 3.05–5.31%, $I^2 = 99.32\%$); overt, 0.65% (95% CI 0.38–0.99%, $I^2 = 96.67\%$); and total, 4.70% (95% CI 2.98–6.79%, $I^2 = 99.53\%$). According to the sensitivity analysis, the prevalence of hypothyroidism tends to be higher in female patients, in those aged ≥65 years, among studies with lower sample sizes, in those with thyroid-stimulating hormone levels <4.5 mIU/L, and in Eastern and Southern Europe. ***Conclusions:*** The current evidence suggests that a considerable proportion of the European population has hypothyroidism, particularly subclinical hypothyroidism, which is undiagnosed. This issue deserves further investigation because of possible deleterious consequences for public health.

Introduction

Hypothyroidism is a condition of thyroid hormone deficiency which is essentially defined based on biochemical parameters. Overt hypothyroidism is the combination of an elevated level of serum thyroid-stimulating

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hormone (TSH) with a decreased level of serum free thyroxin (fT_4) as compared to the reference ranges in the general population. Subclinical hypothyroidism is defined as an elevated serum TSH level in combination with a normal serum fT_4 level [1, 2]. The reference ranges for TSH and fT_4 currently used to define thyroid dysfunction are subject of discussion because of the arbitrary nature of the cutoffs. This issue is of clinical importance for diagnosis and treatment decision purposes [1, 3].

The prevalence of hypothyroidism varies considerably across the general population. There is a number of factors that can influence the prevalence of this condition. For example, the occurrence of hypothyroidism is affected by differences in the iodine status between populations, with higher prevalence among those with high iodine intake and in severely iodine-deficient populations [4]. The prevalence of hypothyroidism is also higher in women, in senior populations, and in Caucasian individuals [5–9]. Furthermore, there is an increased risk of hypothyroidism in patients with autoimmune diseases, including diabetes mellitus, rheumatoid arthritis, or systemic lupus erythematosus, and also in patients with other conditions, such as HIV infection [10–14].

Several studies have been conducted to estimate the prevalence of hypothyroidism. The estimates can vary between 0.1 and 12.5%, depending on the definition used [15, 16]. For example, some studies evaluated the prevalence of undiagnosed and untreated subclinical and/or overt hypothyroidism [17–19], while others addressed previously diagnosed and treated hypothyroidism [20, 21]. Patients with undiagnosed hypothyroidism are not treated for the disease and therefore might be at higher risk of developing long-term complications, such as serious and even fatal cardiovascular diseases, diabetes, or others [22–25]. This situation may result in important implications for public health. Although a systematic review with a meta-analysis on the European prevalence and incidence of (undiagnosed and diagnosed) thyroid dysfunction has been published, that work considered only studies that reported simultaneously on both hypo- and hyperthyroidism. This approach led to the exclusion of studies that exclusively addressed hypothyroidism. Furthermore, several studies were concluded after the publication of that meta-analysis [26]. Therefore, there is rationale to perform a systematic review and meta-analysis aiming to determine the prevalence of undiagnosed hypothyroidism in Europe.

Methods

This study conforms to standard guidelines and was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [27]. Online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000499751) presents the PRISMA checklist.

Search Strategy

The Medline, EMBASE, and Cochrane Central databases were searched for articles published between January 2008 and April 2018. Bibliographic reference lists of all relevant studies, meta-analyses, and systematic reviews were hand searched to identify additional eligible articles. The electronic database search strategy is available in online supplementary Tables 2 and 3.

Study Selection

The titles and abstracts of all retrieved citations were screened by two independent reviewers (D.M. and C.A.) to identify potentially relevant publications. Full texts were retrieved for relevant citations. Discrepancies were resolved by majority decision (two of three) involving a third investigator (F.B.M.).

Studies were included if they met the following criteria: (1) based on a European population, (2) included participants from the general population (without age or sex restrictions) without previously known thyroid disease, (3) provided epidemiological data on the prevalence of subclinical, overt, and/or total hypothyroidism, and (4) provided definitions for subclinical and overt hypothyroidism according to laboratory measurements, namely TSH and fT_4 levels. Studies involving only participants with underlying diseases (e.g., diabetes) or conditions (e.g., pregnancy) were excluded. Reviews, case reports, abstracts, and conference proceedings were excluded. No further exclusion criteria were applied.

Data Extraction

Data were extracted by two independent reviewers (D.M. and C.A.). The data retrieved from each study included first author's name, bibliographic reference, year of publication, country/region, study design, demographic characteristics (mean age, proportion of females, number of subjects included), prevalence of hypothyroidism, reference ranges for thyroid function tests and thyroid disorder categories, as well as assays used to measure thyroid function in each study.

Evaluation of Methodological Quality

The Newcastle-Ottawa Scale was used to assess the methodological quality of the included studies. This scale considers the following: selection of the study groups, comparability of the groups, and ascertainment of either the exposure (for case-control studies) or outcome of interest (for cohort studies) [28]. A maximum of 1 point for each item within the "selection" and "exposure/outcome" categories could be awarded. For the "comparability" category, a maximum of 2 points could be awarded. The summary score equals the number of points earned by each study, totaling a maximum of 9 (maximum of 8 points for cross-sectional analysis). An adapted form of the Newcastle-Ottawa Scale was used to assess cross-sectional studies [29]. Studies scoring ≥7 points were considered to be of good quality, those scoring <7 and ≥5 points were considered to be of moderate quality, and those scoring <5 points were considered to be of poor quality.

Statistical Analysis

The co-primary outcomes were the proportion of people with undiagnosed (1) subclinical, (2) overt, and (3) total hypothyroidism (i.e., the sum of subclinical and overt cases). The classification of cases as subclinical or overt hypothyroidism was the one provided by the authors of the studies included in this systematic review.

Pooled estimates of proportions with corresponding 95% confidence intervals (CIs) were calculated using the "exact" method within a random-effects model [30, 31]. Between-study heterogeneity was assessed using the χ^2 test and the I^2 measure of inconsistency [32]. An I^2 estimate >50% was considered indicative of substantial heterogeneity. Publication bias was evaluated by Egger's regression asymmetry test and visually examined by a funnel plot [33]. All reported p values are two-sided with significance being set as <0.05. A sensitivity analysis was carried out to test the influence of sex (male vs. female), age (mean age <65 years vs. ≥65 years), TSH reference values for determining hypothyroidism (<4.5 mIU/L vs. ≥4.5 mIU/L), the sample size of the studies (number of patients <1,000 vs. 1,000–10,000 vs. >10,000), and geographic region (Northern, Southern, Western, and Eastern Europe) on the estimates of prevalence. All statistical analyses were performed in STATA version 13 (StataCorp, 2013).

Results

Included Studies

Figure 1 presents the search strategy flowchart. The search returned 15,565 citations. After excluding 4,526 duplicates and 11,003 studies based on revision of titles and abstracts, 36 full-text articles were assessed for eligibility. Of those, 20 articles were selected. One article reported results for two populations [15].

Study Characteristics

Table 1 presents the main characteristics of the studies selected for systematic review. The sample size of selected studies varied between 307 [34] and 80,490 [35]. The studies included sample populations from Austria [35], Belgium [36], Bulgaria [37], Denmark [38], Germany [39, 40], Italy [16, 18, 41], Norway [15, 42], Spain [17, 19, 34, 43], The Netherlands [44, 45], the UK [46, 47], and Turkey [48].

The report of selected articles results from cross-sectional analysis of 8 population-based surveys [15–18, 40–42, 49], 7 prospective cohort studies [34, 38, 39, 44–47], 2 retrospective cohort studies [35, 36], and 3 case-control studies [37, 43, 48].

The conceptual definition of subclinical hypothyroidism (elevated TSH and normal free thyroid hormone) and overt hypothyroidism (elevated TSH and low free thyroid hormone) was the same across the selected studies, but the reference ranges for TSH and free thyroid hormones (i.e., fT_4 and/or fT_3) were not. The highest limit of the reference range for TSH varied between 3.4 mIU/L [40] and 5.5 mIU/L [48]. The lowest limits of the reference ranges varied between 8.0 pmol/L [42] and 12.8 pmol/L [40] for fT_4 and between 2.96 pmol/L [48] and 3.92 pmol/L [40] for fT_3.

Risk of Bias in Selected Studies

The studies' methodological quality scores are available in online supplementary Tables 4–6. All cohort studies (n = 9), 2 case-control studies, and 3 cross-sectional studies were considered to have good methodological quality; 1 case-control study and 5 cross-sectional studies were considered to have moderate quality.

Prevalence of Undiagnosed Hypothyroidism

The prevalence of undiagnosed hypothyroidism in European countries is presented in Table 2.

With the exception of one study [15], all studies reported the prevalence of undiagnosed subclinical hypothyroidism, which varied between 0.5% in Germany [39, 50] and 12.5% in Italy [16].

The prevalence of undiagnosed overt hypothyroidism was reported in 11 studies [15–19, 40–43, 46, 48] and varied between 0.1% in Norway [15] and 3.2% in Germany [46].

The prevalence of undiagnosed total (subclinical plus overt) hypothyroidism was ascertained in 11 studies [15–19, 40–43, 46, 48], with estimates ranging between 2.7% [41] and 12.8% [16]. The prevalence of hypothyroidism was lower in men than in women for subclinical (men: min. 0.9%, max. 8.5%; women: min. 2.8%, max. 16.9%), overt (men: min. 0.0%, max. 0.3%; women: min. 0.5%, max. 0.9%), and total hypothyroidism (men: min. 1.2%, max. 8.5%; women: min. 3.8%, max. 17.5%).

Meta-Analysis

The estimated prevalence of undiagnosed subclinical hypothyroidism was 4.11% (95% CI 3.05–5.31%, p < 0.001, I^2 = 99.32%) (Fig. 2). The prevalence of undiagnosed overt hypothyroidism was 0.65% (95% CI 0.38–0.99%, p < 0.001, I^2 = 96.67%) (Fig. 3). Undiagnosed total hypothyroidism was estimated with a prevalence of 4.70% (95% CI 2.98–6.79%, p < 0.001, I^2 = 99.53%) (Fig. 4).

The funnel plots (for studies studying subclinical, overt, and total hypothyroidism) appear asymmetric, with smaller studies tending to report larger proportions of hypothyroidism, which may suggest publication bias (online suppl. Fig. 1–3). Egger's regression asymmetry

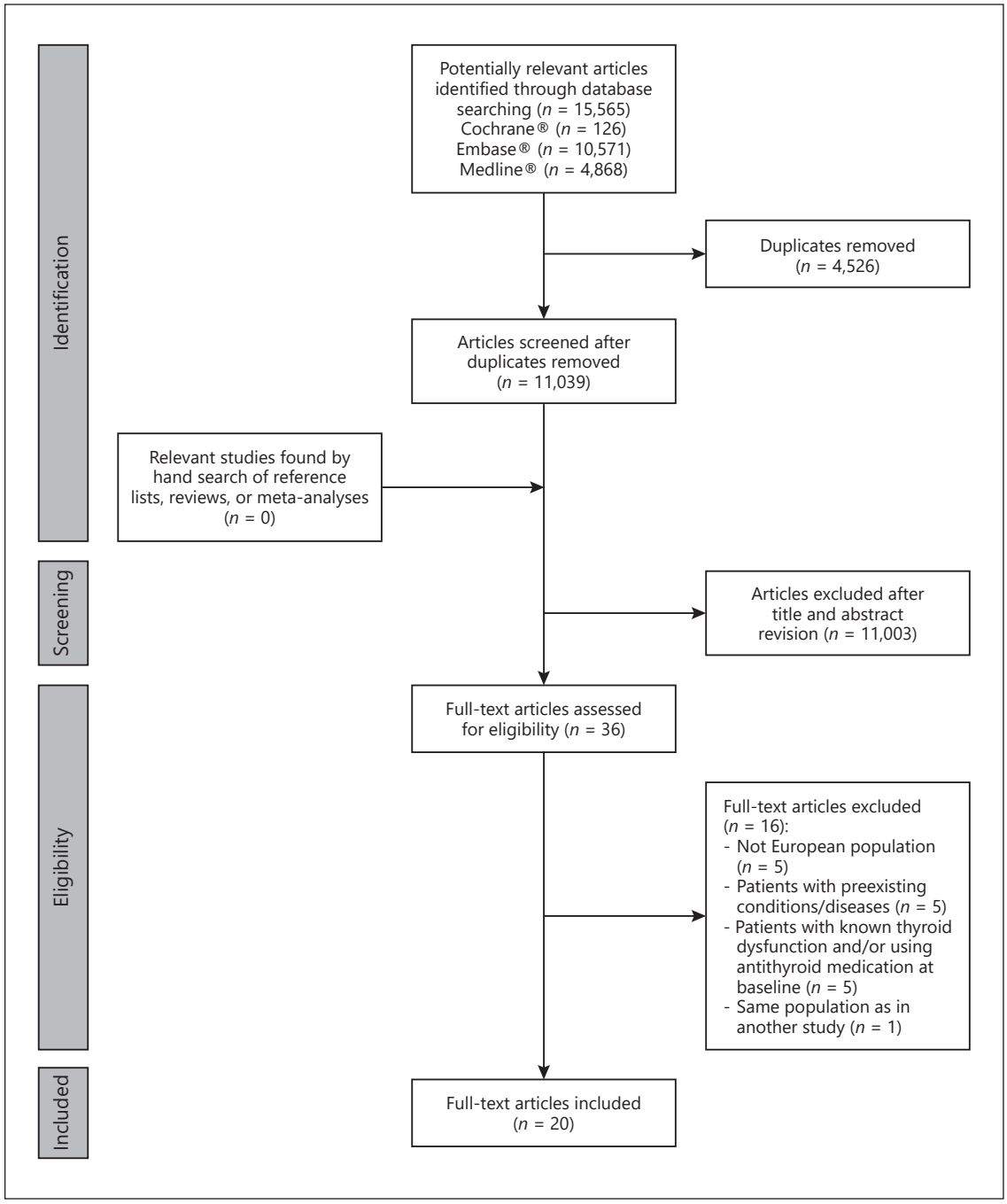

Fig. 1. Flowchart of study selection in the systematic review.

test detected publication bias among the studies included to assess the proportion of overt hypothyroidism, but not among the subclinical or total hypothyroidism analysis (subclinical hypothyroidism: coefficient 6.06, standard error 3.56, $p = 0.105$; overt hypothyroidism: coefficient 4.00, standard error 1.46, $p = 0.021$; total hypothyroidism: coefficient 9.43, standard error 4.45, $p = 0.06$). The test provides weak evidence for the presence of small-study effects. However, there is evidence of substantial heterogeneity among the results of the three proportion esti-

Table 1. Main characteristics of studies selected for systematic review

Study (first author)	Location	Period	Design	Characteristics of the source population	Participants, *n*	Participants' age, years	Definition of hypothyroidism	Assays
Heeringa, 2008 [44][1]	Rotterdam, The Netherlands	1990	cross-sectional analysis within a prospective cohort study (The Rotterdam Study)	all residents of the Rotterdam suburb of Ommoord, The Netherlands, aged ≥55 years	T: 1,607; M: 632 (39.3%); F: 975 (60.7%)	median (range): 68 (55–93)	SH: TSH >4.5 and <19.9 mIU/L, fT_4 in the reference range[1]	TSH: Lumitest, Henning, Berlin, Germany; fT_4: Vitros ECi Immunodiagnostic System, Ortho-Clinical Diagnostics, Amersham, UK
Hogervorst, 2008 [46]	UK (England and Wales)	1998	cross-sectional analysis within a prospective cohort study (MRC-CFAS)	subset of respondents originally recruited for the MRC-CFAS aged ≥65 years	T: 1,047; M: 513 (49.0%); F: 534 (51.0%)	mean ± SD: 73.6±6.2	OH: TSH >4.8 mIU/L, fT_4 <13 pmol/L; SH: TSH >4.8 IU/L, fT_4 = 13–23 pmol/L	TSH: enzyme-amplified immunometric assay kit (Novobiolabs Ltd., Cambridge, UK); fT_4: analogue radioimmunoassay kit (Amerlex-M, Kodak, Amersham, UK)
Ceresini, 2009 [41][2]	Italy	1998	cross-sectional analysis	community-dwelling adults aged ≥65 years living in Tuscany, Italy	T: 1,171; M: 519 (44.3%); F: 652 (55.7%)	mean ± SD: 75.3±7.3 (800 euthyroid participants)	OH: TSH >4.68 mIU/L, fT_4 <10.04 pmol/L; SH: TSH >4.68 mIU/L, fT_4 = 9.91–28.19 pmol/L	TSH/fT_4: chemiluminescent immunoassay (Vitros Reagent, Ortho-Clinical Diagnostics, Johnson and Johnson Medical Section, Milan, Italy)
Ittermann, 2010 [39][1]	Pomerania, Germany	1997–2001	cross-sectional analysis within a prospective cohort study	adults aged 20–79 years living in West Pomerania, Germany	T: 2,339; M: 1,148 (49.1%); F: 1,191 (50.9%)	median (range): 45 (20–85)	SH: TSH >4.5 and <19.9 mIU/L, fT_4 in the reference range[1]	TSH/fT_4: immunochemiluminescent procedures (LIA-mat, Byk Sangtec Diagnostica GmbH, Frankfurt, Germany)
Lucas, 2010 [17][3]	Catalonia, Spain	2001	cross-sectional study within the Health Survey of Catalonia (based on interviewer-directed questionnaires with 165 items)	nonhospitalized adults aged 18–74 years living in Catalonia, Spain	T: 1,124; M: 500 (44.5%); F: 624 (55.5%)	mean ± SD: 44.8±15.2	OH: TSH >4 mIU/L, fT_4 <10.30 pmol/L; SH: TSH >4 mIU/L, fT_4 = 10.30–24.46 pmol/L	TSH: Immulite Third Generation TSH Chemiluminescent Enzyme Immunoassay; fT_4: Immulite fT_4 Chemiluminescent Enzyme Immunoassay; all from DPC, Los Angeles, CA, USA
Asvold, 2011 [42] (HUNT 1)	Nord-Trøndelag, Norway	1995–1997	cross-sectional analysis within a survey (comprehensive questionnaires, clinical examination, blood sampling, and thyroid function measurements)	all adults living in Nord-Trøndelag county in Norway	T: 29,480; M: 9,769 (33.1%); F: 19,711 (66.9%)	median (range): 57 (41–98)	OH: TSH >4.0 mIU/L, fT_4 <8.0 pmol/L; SH: TSH = 3.6–4.0 mIU/L, or TSH >4.0 mIU/L and fT_4 ≥8.0 pmol/L	TSH: DELFIA hTSH Ultra Kit; fT_4: DELFIA fT_4 Kit; all from Wallac Oy, Turku, Finland
Schultz, 2011 [38]	Copenhagen, Denmark	1998–2000	cross-sectional analysis within a survey (comprehensive questionnaires, clinical examination, blood sampling, and thyroid function measurements)	participants aged 50–91 years recruited from the general population in Frederiksberg, Copenhagen, Denmark	T: 605; M: 253 (41.8%); F: 352 (58.2%)	mean ± SD: 68.0±10.7	SH: TSH >4.0 mIU/L, fT_4 in the reference range	TSH: immunoradiometric method (RIA-GNOST, Behringwerke AB, Marburg, Germany); fT_4: solid-phase, chemiluminescent, competitive immunoassay (Immulite 2500)
de Jongh, 2011 [45]	The Netherlands	1992–1993	cross-sectional analysis within a prospective cohort study	individuals aged 55–85 years included in LASA	T: 1,219; M: 603 (49.5%); F: 616 (50.5%)	mean ± SD: 75.5±6.6	SH: TSH >4.5 mIU/L, fT_4 = 11–22 pmol/L, fT_3 = 3.5–6.5 pmol/L	TSH: RIA (Centaur, Bayer Diagnostics); fT_4: competitive immunoassay (Centaur, Bayer Diagnostics)
Dişel, 2012 [48][3]	Adana, Turkey	2008–2009	cross-sectional analysis within a case-control study (cancer patients vs. healthy people)	healthy people (age- and sex-matched control group for cancer patients)	T: 373; M: 198 (53.1%); F: 175 (46.9%)	mean (95% CI) = 55.6 (54.2–57.0)	OH: TSH >5.5 mIU/L, fT_4 <9.52 pmol/L, fT_3 <2.96 pmol/L; SH: TSH >5.5 mIU/L, fT_4 = 9.52–19.56 pmol/L, fT_3 = 2.96–5.40 pmol/L	TSH/fT_4: third-generation chemiluminescent immunoassay (ADVIA Centaur, Siemens Diagnostic)
Díez, 2012 [43]	Segovia, Spain	2004–2010	cross-sectional analysis within a case-control study (diabetic patients vs. healthy people)	control group in the study, patients without diabetes nor known thyroid diseases	T: 911; M: 332 (36.4%); F: 579 (63.6%)	mean ± SD: 57.4±16.1	OH: TSH >5 mIU/L, fT_4 <9 pmol/L; SH: TSH >5 mIU/L, normal fT_4	TSH/fT_4: immunochemiluminescent assay (Immulite, Diagnostic Products, Los Angeles, CA, USA)
Resta, 2012 [16][3]	Bari, Italy	2008–2010	cross-sectional analysis	patients aged 64–86 years attending a geriatric service of the University of Bari	T: 337; M: 177 (52.5%); F: 160 (47.5%)	mean ± SD: 74.3±5.8	OH: TSH >3.6 mIU/L, fT_4 <10.30 pmol/L; SH: TSH >3.6 mIU/L, fT_4 = 10.30–21.88 pmol/L	TSH/fT_4: commercial kits (DiaSorin S.p.A., Saluggia, Italy)
Asvold, 2013 [15] (HUNT 2)[2]	Nord-Trøndelag, Norway	1995–1997	cross-sectional analysis within a survey (comprehensive questionnaires, clinical examination, blood sampling, and thyroid function measurements)	adult residents in the Nord-Trøndelag county	T: 33,917; M: 10,643 (31.4%); F: 23,274 (68.6%)	median (range): 49 (36–64)	OH: TSH >4.5 mIU/L, fT_4 <8 pmol/L; SH: TSH >4.5 mIU/L, fT_4 = 8–20 pmol/L	TSH: DELFIA hTSH Ultra Kit; fT_4: DELFIA fT_4 Kit; all from Wallac Oy, Turku, Finland

Table 1 (continued)

Study (first author)	Location	Period	Design	Characteristics of the source population	Participants, *n*	Participants' age, years	Definition of hypothyroidism	Assays
Asvold, 2013 [15] (HUNT 3)[2]	Nord-Trøndelag, Norway	2006–2008	cross-sectional analysis within a survey (comprehensive questionnaires, clinical examination, blood sampling, and thyroid function measurements)	adult residents in the Nord-Trøndelag county	T: 49,180; M: 22,358 (45.5%); F: 26,822 (54.5%)	median (range): 53 (40–64)	OH: TSH >4.5 mIU/L, fT_4 <8 pmol/L; SH: TSH >4.5 mIU/L, fT_4 = 9–19 pmol/L	TSH: DELFIA hTSH Ultra Kit; fT_4: DELFIA fT_4 Kit; all from Wallac Oy, Turku, Finland
Delitala, 2014 [18][3]	Sardinia, Italy	2001	cross-sectional analysis within the Sardinian survey	participants in the Sardinian survey	T: 6,252; M: 2,826 (45.2%); F: 3,426 (54.8%)	median (range): 41.7 (28.8–57)	OH: TSH >4.0 mIU/L, fT_4 <11.46 pmol/L; SH: TSH >4.0 mIU/L, fT_4 = 11.46–22.65 pmol/L	TSH/fT_4: automated chemiluminescence assay system (Immulite 2000, Erlangen, Germany)
Formiga, 2013 [34]	Barcelona, Spain	2009	cross-sectional analysis within a prospective cohort study	subjects from the follow-up prospective cohort study of participants from the OCTABAIX study	T: 307; M: 123 (45.4%); F: 184 (54.6%)	N/A	OH: TSH >5 mIU/L, fT_4 <10 pmol/L; SH: TSH >5 mIU/L, fT_4 = 10–26 pmol/L	TSH/fT_4: electrochemiluminescence immunoassay based on the sandwich principle with MABs (Roche Diagnostics)
Kovar, 2015 [35][3]	Vienna, Austria	1993–2004	cross-sectional analysis within a retrospective cohort study	individuals aged ≥18 years admitted to the Institute of Medical and Chemical Laboratory Diagnostics of the Medical University of Vienna, Austria; fT_4 values within normal range	T: 80,490; M: 31,577 (39.2%); F: 48,913 (60.8%)	median (range): 48 (34–61)	SH: TSH >4.5 and >20.0 mIU/L, fT_4 = 9.01–21.88 pmol/L	TSH/fT_4: electrochemiluminescence immunoassays "ECLIA" (Elecsys 2010 and Modular Analytics E170, respectively, Roche Diagnostics, Mannheim, Germany)
Ludwig, 2015 [40]	Leutkirch, Germany	2002	population-based cross-sectional study based on a standardized questionnaire and documentation of physical, biochemical, and ultrasonographic findings	individuals aged ≥18 years living in Leutkirch, Germany who participated in the EMIL study	T: 1,276; M: 674 (52.8%); F: 602 (47.2%)	mean ± SD: 40.7±12.7	OH: TSH ≥3.4 mIU/L, fT_4 <12.8 pmol/L; SH: TSH ≥3.4 mIU/L, fT_4 = 12.8–20.4 pmol/L, fT_3 = 3.92–6.74 pmol/L	TSH/fT_4: Elecsys® 2010 Disk and Rack Analyzers (Roche Diagnostics, Indianapolis, IN, USA)
Pfister, 2015 [47][1]	Norfolk, UK	1993–1997	cross-sectional analysis within a prospective cohort study	adults aged 40–79 years living in Norfolk, England	T: 11,642; M: 5,461 (46.9%); F: 6,181 (53.1%)	median (range): 58 (39–78)	SH: TSH >4.5 and <19.9 mIU/L, fT_4 in the reference range[1]	N/A
Valdés, 2017 [19]	Spain	2009–2010	cross-sectional, population-based survey	adults aged ≥18 years living in Spain	T: 4,554; M: 1,932 (42.4%); F: 2,622 (57.6%)	median (range): 50 (18–93)	OH: TSH >5.0 mIU/L, fT_4 <11.0 pmol/L; SH: TSH >5.0 mIU/L, fT_4 ≥11.0 pmol/L	TSH/fT_4: electrochemiluminescence immunoassay (Modular Analytics E170, cobas e 602; Roche Diagnostics, Basel, Switzerland)
Veltri, 2017 [36]	Brussels, Belgium	2015	cross-sectional analysis within a retrospective cohort study	individuals aged ≥20 years living in Brussels	T: 676; M: 151 (22.3%); F: 525 (77.7%)	mean ± SD: 44.2±15.3	SH: TSH >4.0 mIU/L, fT_4 in the reference range	TSH/fT_4: chemiluminescence Centaur XP Siemens immunoanalyzer
Elenkova, 2017 [37]	Sofia, Bulgaria	2009–2012	cross-sectional analysis within a case-control study	control group in a case-control study: healthy women aged ≥18 years	T: 106; M: 0 (0.0%); F: 106 (100%)	mean ± SD: 35.5±8.46	OH: TSH >4.0 mIU/L, fT_4 <10.0 pmol/L; SH: TSH >4.0 mIU/L, fT_4 ≥10.0 pmol/L	TSH/fT_4: commercial kits produced by BRAHMS GmbH, Germany

CI, confidence interval; EMIL, Echinococcus Multilocularis Infection and other medical disorders in Leutkirch; F, female; LASA, Longitudinal Aging Study Amsterdam; M, male; MRC-CFAS, Medical Research Council Cognitive Function and Ageing Study; N/A, not available; OH, overt hypothyroidism; SD, standard deviation; SH, subclinical hypothyroidism; T, total; TSH, thyroid-stimulating hormone. [1] According to Baumgartner et al. [50]. [2] Patients aged >65 years. [3] Units for reference ranges for fT_4 (ng/dL) and/or fT_3 (pg/mL) originally presented in the study were converted to SI units (pmol/L).

mates, which makes the publication bias analysis difficult. Moreover, there are studies reporting a reduced number of events, particularly in the estimation of overt hypothyroidism, which can lead to false-positive publication bias test results.

Sensitivity Analysis

Table 3 presents the results of the sensitivity analysis. In general, the prevalence of hypothyroidism tends to be higher in female patients, those aged ≥65 years, among studies with lower sample sizes, in case of TSH reference levels <4.5 mIU/L, and in Eastern and Southern Europe.

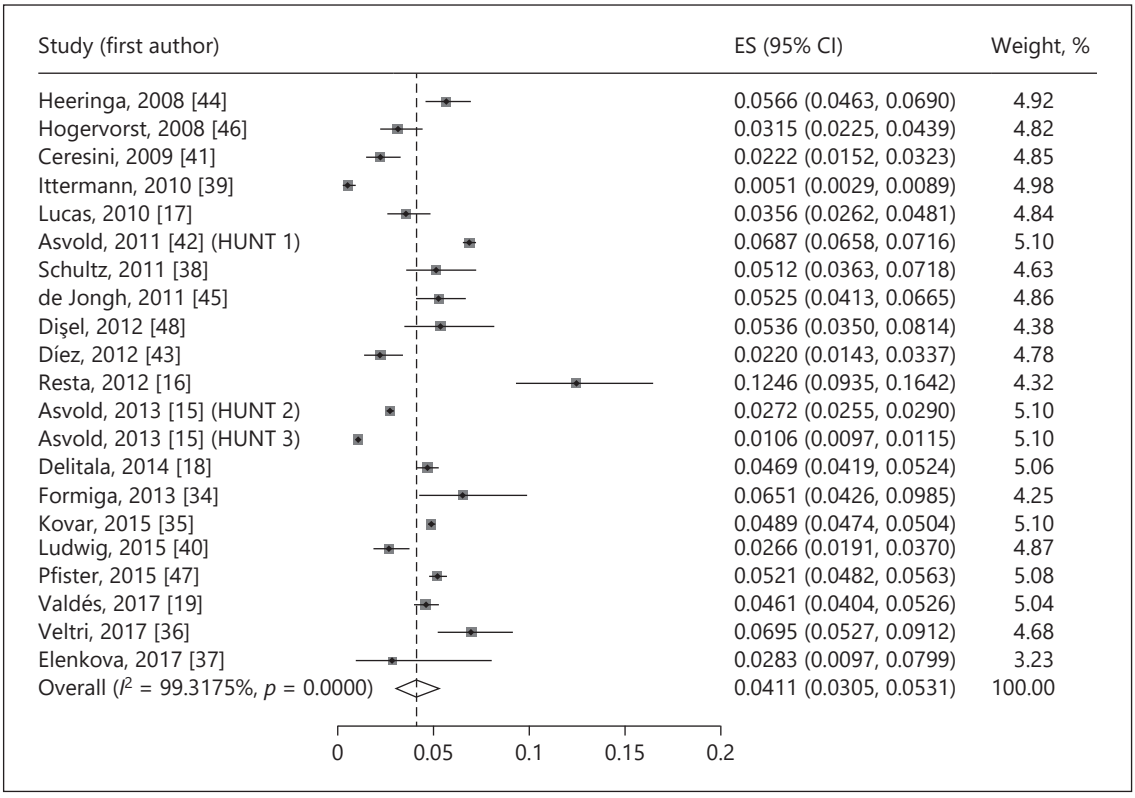

Fig. 2. Prevalence of undiagnosed subclinical hypothyroidism. ES, estimate of proportions; CI, confidence interval.

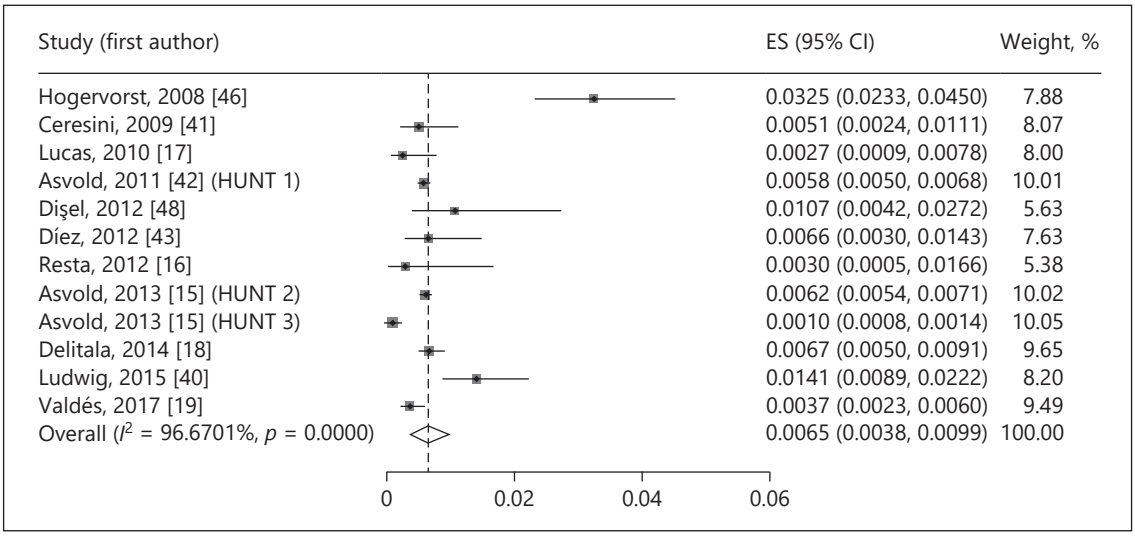

Fig. 3. Prevalence of undiagnosed overt hypothyroidism. ES, estimate of proportions; CI, confidence interval.

Table 2. Prevalence of undiagnosed hypothyroidism in European countries

Study	Location	Period	Sex	Source population		Undiagnosed hypothyroidism					
						subclinical		overt		total	
				n	%	*n*	%	*n*	%	*n*	%
Heeringa, 2008 [44][1]	Rotterdam, The Netherlands	1990	M	632	39.3	–		–		–	
			F	975	60.7	–		–		–	
			T	1,607	100	91	5.7	–		–	
Hogervorst, 2008 [46]	UK (England and Wales)	1998	M	513	49.0	–		–		–	
			F	534	51.0	–		–		–	
			T	1,047	100	33	3.2	34	3.2	67	6.4
Ceresini, 2009 [41]	Italy	1998	M	519	44.3	–		–		–	
			F	652	55.7	–		–		–	
			T	1,171	100	26	2.2	6	0.5	32	2.7
Ittermann, 2010 [39][1]	Pomerania, Germany	1997–2001	M	1,148	49.1	–		–		–	
			F	1,191	50.9	–		–		–	
			T	2,339	100	12	0.5	–		–	
Lucas, 2010 [17]	Catalonia, Spain	2001	M	500	44.5	18	3.6	0	0.0	18	3.6
			F	624	55.5	22	3.5	3	0.5	25	4.0
			T	1,124	100	40	3.5	3	0.2	43	3.8
Asvold, 2011 [42] (HUNT 1)	Nord-Trøndelag, Norway	1995–1997	M	9,769	33.1	–		–		–	
			F	19,711	66.9	–		–		–	
			T	29,480	100	2,024	6.9	172	0.6	2,196	7.4
Schultz, 2011 [38]	Copenhagen, Denmark	1998–2000	M	253	41.8	5	2.0	–		–	
			F	352	58.2	26	7.4	–		–	
			T	605	100	31	5.1	–		–	
de Jongh, 2011 [45]	The Netherlands	1992–1993	M	603	49.5	–		–		–	
			F	616	50.5	–		–		–	
			T	1,219	100	64	5.3	–		–	
Dişel, 2012 [48]	Adana, Turkey	2008–2009	M	198	53.1	–		–		–	
			F	175	46.9	–		–		–	
			T	373	100	20	5.4	4	1.1	24	6.4
Díez, 2012 [43]	Segovia, Spain	2004–2010	M	332	36.4	3	0.9	1	0.3	4	1.2
			F	579	63.6	17	2.9	5	0.9	22	3.8
			T	911	100	20	2.2	6	0.7	26	2.9
Resta, 2012 [16]	Bari, Italy	2008–2010	M	177	52.5	15	8.5	0	0.0	15	8.5
			F	160	47.5	27	16.9	1	0.6	28	17.5
			T	337	100	42	12.5	1	0.3	43	12.8
Asvold, 2013 [15] (HUNT 2)[2, 3]	Nord-Trøndelag, Norway	1995–1997	M	10,643	31.4	224	2.1	21	0.2	245	2.3
			F	23,274	68.6	698	3.0	186	0.8	884	3.8
			T	33,917	100	922	2.7	207	0.6	1,129	3.3
Asvold, 2013 [15] (HUNT 3)[2, 3]	Nord-Trøndelag, Norway	2006–2008	M	22,358	45.5	224	1.0	22	0.1	246	1.1
			F	26,822	54.5	295	1.1	27	0.1	322	1.2
			T	49,180	100	519	1.1	49	0.1	568	1.2
Delitala, 2014 [18]	Sardinia, Italy	2001	M	2,826	45.2	–		–		–	
			F	3,426	54.8	–		–		–	
			T	6,252	100	293	4.7	42	0.7	335	5.4
Formiga, 2013 [34]	Barcelona, Spain	2009	M	123	45.4	9	7.3	–		–	
			F	184	54.6	11	6.0	–		–	
			T	307	100	20	6.5	–		–	

Table 2 (continued)

Study	Location	Period	Sex	Source population		Undiagnosed hypothyroidism					
						subclinical		overt		total	
				n	%	*n*	%	*n*	%	*n*	%
Kovar, 2015 [35]	Vienna, Austria	1993–2004	M	31,577	39.2	868	2.7	–		–	
			F	48,913	60.8	3,066	6.3	–		–	
			T	80,490	100	3,934	3.7	–		–	
Ludwig, 2015 [40]	Leutkirch, Germany	2002	M	674	52.8	–		–		–	
			F	602	47.2	–		–		–	
			T	1,276	100	34	2.7	18	1.4	52	4.1
Pfister, 2015 [47][1]	Norfolk, UK	1993–1997	M	5,461	46.9	–		–		–	
			F	6,181	53.1	–		–		–	
			T	11,642	100	607	5.2	–		–	
Valdés, 2017 [19]	Spain	2009–2010	M	1,932	42.4	65	3.4	1	0.1	66	3.4
			F	2,622	57.6	145	5.5	16	0.6	161	6.1
			T	4,554	100	210	4.6	17	0.3	227	5.0
Veltri, 2017 [36]	Brussels, Belgium	2015	M	151	22.3	–		–		–	
			F	525	77.7	–		–		–	
			T	676	100	47	6.9	–		–	
Elenkova, 2017 [37]	Sofia, Bulgaria	2009–2012	M	0	0.0	–		–		–	
			F	106	100	3	2.8	–		–	
			T	106	100	3	2.8	–		–	

M, male; F, female; T, total. [1] Data obtained from Baumgartner et al. [50]. [2] Table presents data from Asvold et al. [15]. Fleiner et al. [81] reported results for untreated total hypothyroidism in patients without diabetes from HUNT 2 (men, 2.2%; women, 3.7%; both sexes, 3.7%) and HUNT 3 (men, 1.2%; women, 1.3%; both sexes, 1.2%). [3] Absolute values were calculated based on percentages.

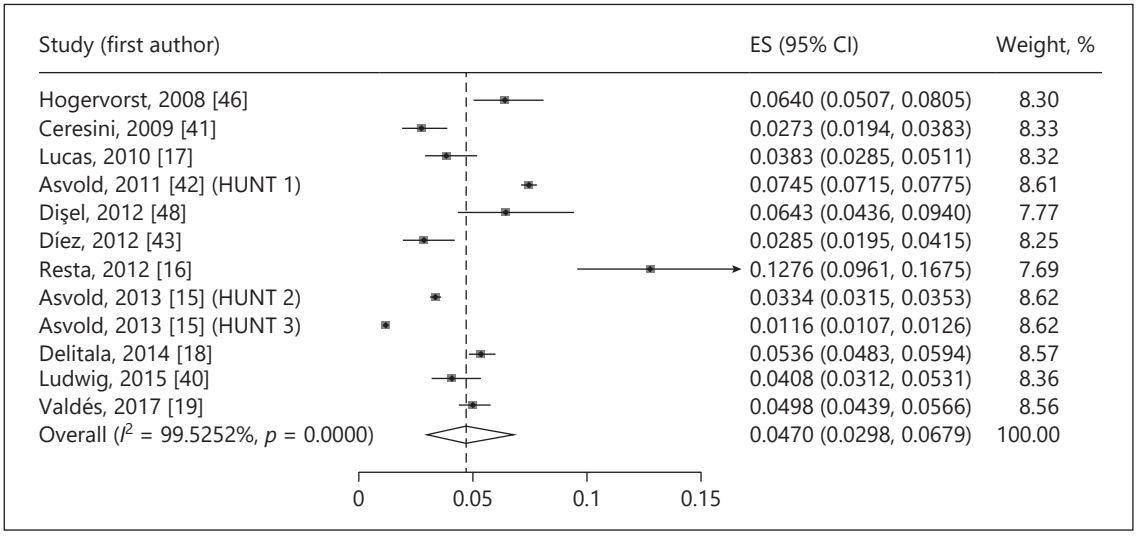

Fig. 4. Prevalence of undiagnosed total hypothyroidism. ES, estimate of proportions; CI, confidence interval.

Table 3. Prevalence of hypothyroidism according to the results obtained in the sensitivity analysis

Variable	Subclinical hypothyroidism	Overt hypothyroidism	Total hypothyroidism
Sex			
Men	2.70% (1.81–3.76%) I^2 = 97.15%*	0.06% (0.01–0.12%) I^2 = 30.37%**	2.67% (1.62–3.96%) I^2 = 96.08%*
Women	4.80% (2.85–7.20%) I^2 = 99.45%*	0.49% (0.11–1.09%) I^2 = 97.13%***	4.83% (2.74–7.46%) I^2 = 99.06%*
Age[1]			
<65 years	3.58% (2.39–4.98%) I^2 = 99.54%*	0.54% (0.29–0.86%) I^2 = 96.67%***	4.16% (2.34–6.48%) I^2 = 99.54%*
≥65 years	5.12% (3.30–7.30%) I^2 = 91.67%*	1.10% (0.03–3.42%) I^2 = 97.00%***	6.60% (2.54–12.35%) I^2 = NR*
Sample size (number of patients)			
<1,000	5.61% (3.40–8.32%) I^2 = 88.65%*	0.64% (0.28–1.11%) I^2 = NR*	6.72% (2.11–13.60%) I^2 = NR*
1,000–10,000	3.37% (2.20–4.77%) I^2 = 95.92%*	0.87% (0.09–1.52%) I^2 = 91.72%*	4.54% (3.73–5.42%) I^2 = 81.41%*
>10,000	3.85% (1.92–6.39%) I^2 = 99.85%*	0.39% (0.01–0.88%) I^2 = NR**	3.54% (0.87–7.93%) I^2 = NR**
TSH reference values			
<4.5 mIU/L	5.34% (3.98–6.88%) I^2 = 94.37%*	0.62% (0.40–0.87%) I^2 = 67.94%*	6.11% (4.48–7.97%) I^2 = 95.70%*
≥4.5 mIU/L	3.46% (2.30–4.85%) I^2 = 99.43%*	0.70% (0.30–1.25%) I^2 = 97.65%*	3.68% (2.22–5.49%) I^2 = 99.10%*
European geographic region			
North	3.75% (1.74–6.47%) I^2 = 99.78%*	0.76% (0.31–1.41%) I^2 = 98.97%*	4.16% (1.48–8.11%) I^2 = 99.86%*
West	3.90% (2.12–6.20%) I^2 = 97.82%*	1.41% (0.89–2.22%) I^2 = NR*	4.08% (3.12–5.31%) I^2 = NR*
East	4.67% (2.91–6.80%) I^2 = NR*	1.07% (0.42–2.72%) I^2 = NR***	6.43% (4.36–9.40%) I^2 = NR*
South	4.50% (3.28–5.91%) I^2 = 91.18%*	0.47% (0.33–0.63%) I^2 = 21.68%*	4.78% (3.52–6.23%) I^2 = 91.38%*

NR, not reported; TSH, thyroid-stimulating hormone. [1] The mean age of patients included in each study was considered. * $p < 0.0001$, ** $p < 0.001$, *** $p < 0.05$.

Discussion

This systematic review and meta-analysis aimed to identify the prevalence of undiagnosed hypothyroidism (subclinical, overt, and total) in the general population of Europe. As we were interested in studying current figures, the time horizon of the search strategy was limited to articles published over the last 10 years. Several studies were dedicated to characterizing the epidemiology of thyroid dysfunctions, but only few addressed the problem of underdiagnosing such diseases [26]. For example, some studies applied drug utilization approaches or electronic health record analysis based on prescriptions data, pharmacy claims, or surveys to identify consumption of antithyroid medication and estimate the prevalence of treated hypothyroidism [21, 51–54]. Furthermore, many studies investigated the prevalence of this disorder or its role as a risk factor for other diseases in specific populations, for example in pregnant women, patients with diabetes, patients with cardiovascular diseases, or immunocompromised individuals [12, 24, 55–59]. Therefore, there is room and need for systematically review of the evidence on the prevalence of undiagnosed hypothyroidism in the general population. As such, patients with known thyroid dysfunction and/or using antithyroid medication at baseline were not considered in this review, as defined in the inclusion criteria.

The present results point out that the current prevalence of undiagnosed subclinical hypothyroidism (4.11%) is higher than the prevalence of undiagnosed overt hypothyroidism (0.65%). This is an unsurprising finding taking into account the conclusions of other studies. A previous meta-analysis on thyroid dysfunctions estimated the mean prevalence of undiagnosed hypothyroidism in Europe at 4.94%, with a clear predominance of the subclinical form of the disease: subclinical hypothyroidism 4.59%, overt hypothyroidism 0.62% [26]. The higher prevalence of subclinical hypothyroidism may be explained by the fact that many patients are asymptomatic or report fewer and milder symptoms than patients with overt hypothyroidism [2]. Furthermore, 75% of patients with subclinical hypothyroidism have a serum TSH level <10 mIU/L (i.e., mild subclinical hypothyroidism) [60], being less prone to hypothyroid symptoms and, for example, cardiovascular events than patients with severe subclinical hypothyroidism [2, 22–24]. Moreover, the TSH concentration usually normalizes within 2 years for 46% of patients with subclinical hypothyroidism if the TSH level is <7 mIU/L in a single measurement [61–63]. Yet, the risk of progression to overt hypothyroidism among patients with severe forms of subclinical hypothyroidism is estimated at 2–6% per year [51, 61, 62].

The results of this meta-analysis should be interpreted with caution given its high heterogeneity (I^2 > 96%). There are considerable differences between the selected studies, including study design (e.g., prospective and retrospective cohort studies, population-based surveys), studied population (e.g., inclusion/exclusion criteria, sex, age), sample size (i.e., range from hundreds to tens of thousands), laboratory tests performed (e.g., TSH, fT_4, fT_3, antibodies), laboratory techniques and material, and reference ranges of circulating thyroid hormones used to diagnose the several forms of hypothyroidism. Despite the limitations of the present meta-analysis, a quantitative synthesis that matches the research question is possibly preferred over qualitative interpretations of results or unclear quasi-quantitative analyses [64]. In addition to the production of overall estimates, meta-analysis provides the advantage of assessing the consistency of findings and improving the understanding of moderator variables, boundary conditions, and generalizability [64–66].

The prevalence of hypothyroidism (both subclinical and overt) was higher in women than in men, which is also in line with previous findings [26]. Monitoring the thyroid status is particularly important in the group of pregnant women or women of childbearing potential since correction of overt hypothyroidism reduces the risk of fetal loss and preterm birth [67, 68]. Treatment of overt hypothyroidism is therefore recommended during pregnancy [69]. Pregnant women with subclinical hypothyroidism before 20 weeks of gestation are at a higher risk of miscarriage [70]. Treatment may reduce miscarriage in thyroid autoantibodies (TPOAb)-positive pregnant women, and therefore women with TSH concentrations >2.5 mIU/L should be evaluated for TPOAb status. Furthermore, TPOAb-positive women with TSH levels greater than the pregnancy-specific ranges as well as women with TPOAb-negative status and TSH levels >10 mIU/L should be treated with levothyroxine. Other subgroups of pregnant women may be considered for treatment depending on TSH levels [69]. Nevertheless, universal thyroid screening in pregnancy is still a matter of debate [71]. The results of randomized controlled trials pointed out that treating pregnant women with subclinical hypothyroidism with levothyroxine provided no benefit on the IQ of the offspring or obstetric outcomes [72, 73]. However, levothyroxine therapy was initiated after the critical phase of fetal brain development, i.e., from the end of the first trimester of pregnancy.

The results of our sensitivity analysis also indicated that the prevalence of any form of hypothyroidism is higher among patients aged ≥65 years (subclinical 5.12%, overt 1.10%) as compared to younger ones (subclinical 3.58%, overt 0.54%). The study by Lucas et al. [17] also illustrates the influence of age on estimates of prevalence: when the authors restricted the analysis to subjects >60 years, the prevalence of subclinical and overt hypothyroidism was estimated at 6.2 and 0.44%, respectively (vs. 3.5 and 0.2% in the general population).

With regards to the reference ranges of serum thyroid hormones, the variation of the highest limit of the reference range for TSH concentration in the studies included in this meta-analysis is considerable (between 3.4 and 5.5 mIU/L) [40, 48]. According to the sensitivity analysis, a higher prevalence of subclinical and total hypothyroidism was found for studies using lower TSH reference values. The most commonly cited reference range for TSH concentration in the clinical literature set the highest limit at 4.0 mIU/L (and the lowest limit at 0.4 mIU/L), while the reference range for fT_4 depends on the type of assay and the population in question [1]. Nevertheless, the reference level cutoffs used to determine overt and subclinical hypothyroidism have changed over the years [46]. Thus, in the context of the present meta-analysis, the lack of consensus on reference ranges for levels of thyroid hormones used to establish diagnoses may result in inaccu-

rate comparisons because of nonoverlapping definitions of disease across the included studies.

Moreover, the sensitivity analysis also detected differences in the prevalence of hypothyroidism depending on the sample sizes of included studies – higher estimates of prevalence among those with lower number of patients – and on the European region – the prevalence of hypothyroidism tended to be higher in Eastern and Southern Europe.

There is great variation in the clinical manifestations of hypothyroidism, ranging from the absence of signs or symptoms to life-threatening conditions, such as myxedema coma [1]. The most common symptoms are nonspecific and vary depending on different individual factors, such as the age or sex of patients. Furthermore, autoimmune hypothyroidism is asymptomatic or associated with only one symptom in nearly 15% of patients with the condition, while 70% of euthyroid individuals have at least one symptom that is usually related with hypothyroidism [74]. These issues may contribute to preclude or at least delay the diagnosis of hypothyroidism. In addition, with the exception of some populations, such as patients with type 1 diabetes mellitus [75, 76], there is no consensus on TSH screening in the general population [1].

The long-term consequences of hypothyroidism are clinically important and adversely affect the health of patients. Those consequences have been mainly studied in patients with subclinical hypothyroidism, given that overt hypothyroidism is usually treated. The body of evidence is particularly robust with regards to the association between hypothyroidism and adverse cardiovascular outcomes. A meta-analysis of individual data on >2,500 elderly participants found that the risk of coronary heart disease and mortality is increased in subjects with higher serum TSH levels [22]. Conversely, patients with TSH concentrations >10 mIU/L are at higher risk of heart failure [22, 23]. Hence, timely diagnosis and treatment initiation are potentially important for preventing adverse consequences of hypothyroidism in patients with the condition. However, the results of a double-blind, randomized, placebo-controlled, parallel-group trial pointed out that giving levothyroxine to senior patients (>65 years) with subclinical hypothyroidism (TSH level 4.60–19.99 mIU/L, fT_4 level within the reference range) provided no significant beneficial effects on thyroid-related quality of life symptoms or cardiovascular events [77]. Other illnesses potentially associated with hypothyroidism include nonalcoholic fatty liver disease, cancer mortality, arthritis, renal failure, and diabetes [25, 78–80].

In conclusion, the current evidence suggests that a considerable proportion of the European population has hypothyroidism, particularly subclinical hypothyroidism, which is not diagnosed. This issue deserves further investigation because of possible deleterious consequences for public health.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

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References

1 Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. Lancet. 2017 Sep; 390(10101):1550–62.
2 Peeters RP. Subclinical Hypothyroidism. N Engl J Med. 2017 Oct;377(14):1404–1404.
3 LeFevre ML; U.S. Preventive Services Task Force. Screening for thyroid dysfunction: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2015 May; 162(9):641–50.
4 Laurberg P, Cerqueira C, Ovesen L, Rasmussen LB, Perrild H, Andersen S, et al. Iodine intake as a determinant of thyroid disorders in populations. Best Pract Res Clin Endocrinol Metab. 2010 Feb;24(1):13–27.
5 Surks MI, Hollowell JG. Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. J Clin Endocrinol Metab. 2007 Dec; 92(12):4575–82.
6 Boucai L, Surks MI. Reference limits of serum TSH and free T4 are significantly influenced by race and age in an urban outpatient medical practice. Clin Endocrinol (Oxf). 2009 May; 70(5):788–93.
7 Vadiveloo T, Donnan PT, Murphy MJ, Leese GP. Age- and gender-specific TSH reference intervals in people with no obvious thyroid disease in Tayside, Scotland: the Thyroid Epidemiology, Audit, and Research Study (TEARS). J Clin Endocrinol Metab. 2013 Mar; 98(3):1147–53.
8 McLeod DS, Caturegli P, Cooper DS, Matos PG, Hutfless S. Variation in rates of autoimmune thyroid disease by race/ethnicity in US military personnel. JAMA. 2014 Apr;311(15): 1563–5.
9 Mammen JS, McGready J, Ladenson PW, Simonsick EM. Unstable Thyroid Function in Older Adults Is Caused by Alterations in Both Thyroid and Pituitary Physiology and Is Associated with Increased Mortality. Thyroid. 2017 Nov;27(11):1370–7.
10 Journy NM, Bernier MO, Doody MM, Alexander BH, Linet MS, Kitahara CM. Hyperthyroidism, Hypothyroidism, and Cause-Specific Mortality in a Large Cohort of Women. Thyroid. 2017 Aug;27(8):1001–10.

11 Emamifar A, Hangaard J, Jensen Hansen IM. Thyroid disorders in patients with newly diagnosed rheumatoid arthritis is associated with poor initial treatment response evaluated by disease activity score in 28 joints-C-reactive protein (DAS28-CRP): an observational cohort study. Medicine (Baltimore). 2017 Oct;96(43):e8357.
12 Domingues SL, Gonçalves FT, Jorge ML, Limongi JE, Ranza R, Jorge PT. High prevalence of hypothyroidism in systemic lupus erythematosus patients without an increase in circulating anti-thyroid antibodies. Endocr Pract. 2017 Nov;23(11):1304–10.
13 Beltran S, Lescure FX, Desailloud R, Douadi Y, Smail A, El Esper I, et al.; Thyroid and VIH Group. Increased prevalence of hypothyroidism among human immunodeficiency virus-infected patients: a need for screening. Clin Infect Dis. 2003 Aug;37(4):579–83.
14 Ji S, Jin C, Höxtermann S, Fuchs W, Xie T, Lu X, et al. Prevalence and Influencing Factors of Thyroid Dysfunction in HIV-Infected Patients. BioMed Res Int. 2016;2016:3874257.
15 Asvold BO, Vatten LJ, Bjøro T. Changes in the prevalence of hypothyroidism: the HUNT Study in Norway. Eur J Endocrinol. 2013 Oct; 169(5):613–20.
16 Resta F, Triggiani V, Barile G, Benigno M, Suppressa P, Giagulli VA, et al. Subclinical hypothyroidism and cognitive dysfunction in the elderly. Endocr Metab Immune Disord Drug Targets. 2012 Sep;12(3):260–7.
17 Lucas A, Julián MT, Cantón A, Castell C, Casamitjana R, Martínez-Cáceres EM, et al. Undiagnosed thyroid dysfunction, thyroid antibodies, and iodine excretion in a Mediterranean population. Endocrine. 2010 Dec; 38(3):391–6.
18 Delitala AP, Pilia MG, Ferreli L, Loi F, Curreli N, Balaci L, et al. Prevalence of unknown thyroid disorders in a Sardinian cohort. Eur J Endocrinol. 2014 Jul;171(1):143–9.
19 Valdés S, Maldonado-Araque C, Lago-Sampedro A, Lillo JA, Garcia-Fuentes E, Perez-Valero V, et al. Population-Based National Prevalence of Thyroid Dysfunction in Spain and Associated Factors: Di@bet.es Study. Thyroid. 2017 Feb;27(2):156–66.
20 Hoogendoorn EH, Hermus AR, de Vegt F, Ross HA, Verbeek AL, Kiemeney LA, et al. Thyroid function and prevalence of anti-thyroperoxidase antibodies in a population with borderline sufficient iodine intake: influences of age and sex. Clin Chem. 2006 Jan;52(1): 104–11.
21 Leese GP, Flynn RV, Jung RT, Macdonald TM, Murphy MJ, Morris AD. Increasing prevalence and incidence of thyroid disease in Tayside, Scotland: the Thyroid Epidemiology Audit and Research Study (TEARS). Clin Endocrinol (Oxf). 2008 Feb;68(2):311–6.
22 Rodondi N, den Elzen WP, Bauer DC, Cappola AR, Razvi S, Walsh JP, et al.; Thyroid Studies Collaboration. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA. 2010 Sep;304(12): 1365–74.
23 Gencer B, Collet TH, Virgini V, Bauer DC, Gussekloo J, Cappola AR, et al.; Thyroid Studies Collaboration. Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. Circulation. 2012 Aug; 126(9):1040–9.
24 Chaker L, Baumgartner C, den Elzen WP, Ikram MA, Blum MR, Collet TH, et al.; Thyroid Studies Collaboration. Subclinical Hypothyroidism and the Risk of Stroke Events and Fatal Stroke: An Individual Participant Data Analysis. J Clin Endocrinol Metab. 2015 Jun; 100(6):2181–91.
25 Gronich N, Deftereos SN, Lavi I, Persidis AS, Abernethy DR, Rennert G. Hypothyroidism is a Risk Factor for New-Onset Diabetes: A Cohort Study. Diabetes Care. 2015 Sep;38(9): 1657–64.
26 Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F, Galofré JC. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. J Clin Endocrinol Metab. 2014 Mar;99(3):923–31.
27 Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009 Aug;151(4):264–9, W64.
28 Wells GA, Tugwell P, O'Connell D, Welch V, Peterson J, Shea B, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
29 Alshabanat A, Zafari Z, Albanyan O, Dairi M, FitzGerald JM. Asthma and COPD Overlap Syndrome (ACOS): A Systematic Review and Meta Analysis. PLoS One. 2015 Sep; 10(9):e0136065.
30 Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. Arch Public Health. 2014 Nov; 72(1):39.
31 DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep; 7(3):177–88.
32 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep;327(7414):557–60.
33 Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Publication bias. In: Rothstein MB, editor. Introduction to meta-analysis. Chichester: John Wiley & Sons; 2009. p. 277–91.
34 Formiga F, Ferrer A, Padros G, Contra A, Corbella X, Pujol R; OCTABAIX Study Group. Thyroid status and functional and cognitive status at baseline and survival after 3 years of follow-up: the OCTABAIX study. Eur J Endocrinol. 2013 Nov;170(1):69–75.
35 Kovar FM, Fang IF, Perkmann T, Haslacher H, Slavka G, Födinger M, et al. Subclinical hypothyroidism and mortality in a large Austrian cohort: a possible impact on treatment? Wien Klin Wochenschr. 2015 Dec;127(23–24):924–30.
36 Veltri F, Rocha FO, Willems D, Praet JP, Grabczan L, Kleynen P, et al. Prevalence of thyroid dysfunction and autoimmunity in the older population and implications of age-specific reference ranges. Clin Chim Acta. 2017 Feb;465:34–9.
37 Elenkova A, Atanasova I, Kirilov G, Natchev E, Ivanova R, Kovatcheva R, et al. Autoimmune hypothyroidism is three times more frequent in female prolactinoma patients compared to healthy women: data from a cross-sectional case-control study. Endocrine. 2017 Sep;57(3):486–93.
38 Schultz M, Kistorp C, Raymond I, Dimsits J, Tuxen C, Hildebrandt P, et al. Cardiovascular events in thyroid disease: a population based, prospective study. Horm Metab Res. 2011 Aug;43(9):653–9.
39 Ittermann T, Haring R, Sauer S, Wallaschofski H, Dörr M, Nauck M, et al. Decreased serum TSH levels are not associated with mortality in the adult northeast German population. Eur J Endocrinol. 2010 Mar;162(3): 579–85.
40 Ludwig U, Holzner D, Denzer C, Greinert A, Haenle MM, Oeztuerk S, et al.; EMIL Study. Subclinical and clinical hypothyroidism and non-alcoholic fatty liver disease: a cross-sectional study of a random population sample aged 18 to 65 years. BMC Endocr Disord. 2015 Aug;15(1):41.
41 Ceresini G, Lauretani F, Maggio M, Ceda GP, Morganti S, Usberti E, et al. Thyroid function abnormalities and cognitive impairment in elderly people: results of the Invecchiare in Chianti study. J Am Geriatr Soc. 2009 Jan; 57(1):89–93.
42 Asvold BO, Bjøro T, Vatten LJ. Association of thyroid function with estimated glomerular filtration rate in a population-based study: the HUNT study. Eur J Endocrinol. 2011 Jan; 164(1):101–5.
43 Díez JJ, Iglesias P. An analysis of the relative risk for hypothyroidism in patients with Type 2 diabetes. Diabet Med. 2012 Dec;29(12): 1510–4.
44 Heeringa J, Hoogendoorn EH, van der Deure WM, Hofman A, Peeters RP, Hop WC, et al. High-normal thyroid function and risk of atrial fibrillation: the Rotterdam study. Arch Intern Med. 2008 Nov;168(20):2219–24.
45 de Jongh RT, Lips P, van Schoor NM, Rijs KJ, Deeg DJ, Comijs HC, et al. Endogenous subclinical thyroid disorders, physical and cognitive function, depression, and mortality in older individuals. Eur J Endocrinol. 2011 Oct; 165(4):545–54.

46 Hogervorst E, Huppert F, Matthews FE, Brayne C. Thyroid function and cognitive decline in the MRC Cognitive Function and Ageing Study. Psychoneuroendocrinology. 2008 Aug;33(7):1013–22.
47 Pfister R, Brägelmann J, Michels G, Wareham NJ, Luben R, Khaw KT. Performance of the CHARGE-AF risk model for incident atrial fibrillation in the EPIC Norfolk cohort. Eur J Prev Cardiol. 2015 Jul;22(7):932–9.
48 Dişel U, Beşen A, Karadeniz C, Mertsoylu H, Sezer A, Köse F, et al. Prevalence of thyroid dysfunction in untreated cancer patients: a cross-sectional study. Med Oncol. 2012 Dec; 29(5):3608–13.
49 Tanno LK, Calderon MA, Goldberg BJ, Gayraud J, Bircher AJ, Casale T, et al. Constructing a classification of hypersensitivity/allergic diseases for ICD-11 by crowdsourcing the allergist community. Allergy. 2015 Jun; 70(6):609–15.
50 Baumgartner C, da Costa BR, Collet TH, Feller M, Floriani C, Bauer DC, et al.; Thyroid Studies Collaboration. Thyroid Function Within the Normal Range, Subclinical Hypothyroidism, and the Risk of Atrial Fibrillation. Circulation. 2017 Nov;136(22):2100–16.
51 Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxf). 1995 Jul; 43(1):55–68.
52 Giorda CB, Carnà P, Romeo F, Costa G, Tartaglino B, Gnavi R. Prevalence, incidence and associated comorbidities of treated hypothyroidism: an update from a European population. Eur J Endocrinol. 2017 May;176(5):533–42.
53 Rodriguez-Gutierrez R, Maraka S, Ospina NS, Montori VM, Brito JP. Levothyroxine overuse: time for an about face? Lancet Diabetes Endocrinol. 2017 Apr;5(4):246–8.
54 Flynn RW, MacDonald TM, Morris AD, Jung RT, Leese GP. The thyroid epidemiology, audit, and research study: thyroid dysfunction in the general population. J Clin Endocrinol Metab. 2004 Aug;89(8):3879–84.
55 Diéguez M, Herrero A, Avello N, Suárez P, Delgado E, Menéndez E. Prevalence of thyroid dysfunction in women in early pregnancy: does it increase with maternal age? Clin Endocrinol (Oxf). 2016 Jan;84(1):121–6.
56 Blumenthal NJ, Byth K, Eastman CJ. Prevalence of thyroid dysfunction and thyroid antibodies in a private obstetrical practice in Sydney. Aust N Z J Obstet Gynaecol. 2016 Jun;56(3):307–11.
57 Song F, Bao C, Deng M, Xu H, Fan M, Paillard-Borg S, et al. The prevalence and determinants of hypothyroidism in hospitalized patients with type 2 diabetes mellitus. Endocrine. 2017 Jan;55(1):179–85.
58 Jia F, Tian J, Deng F, Yang G, Long M, Cheng W, et al. Subclinical hypothyroidism and the associations with macrovascular complications and chronic kidney disease in patients with Type 2 diabetes. Diabet Med. 2015 Aug; 32(8):1097–103.
59 Blum MR, Wijsman LW, Virgini VS, Bauer DC, den Elzen WP, Jukema JW, et al.; PROSPER study group. Subclinical Thyroid Dysfunction and Depressive Symptoms among the Elderly: A Prospective Cohort Study. Neuroendocrinology. 2016;103(3–4):291–9.
60 Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000 Feb;160(4): 526–34.
61 Huber G, Staub JJ, Meier C, Mitrache C, Guglielmetti M, Huber P, et al. Prospective study of the spontaneous course of subclinical hypothyroidism: prognostic value of thyrotropin, thyroid reserve, and thyroid antibodies. J Clin Endocrinol Metab. 2002 Jul;87(7):3221–6.
62 Somwaru LL, Rariy CM, Arnold AM, Cappola AR. The natural history of subclinical hypothyroidism in the elderly: the cardiovascular health study. J Clin Endocrinol Metab. 2012 Jun;97(6):1962–9.
63 Meyerovitch J, Rotman-Pikielny P, Sherf M, Battat E, Levy Y, Surks MI. Serum thyrotropin measurements in the community: five-year follow-up in a large network of primary care physicians. Arch Intern Med. 2007 Jul; 167(14):1533–8.
64 Ioannidis JP, Patsopoulos NA, Rothstein HR. Reasons or excuses for avoiding meta-analysis in forest plots. BMJ. 2008 Jun;336(7658): 1413–5.
65 Smith TC, Spiegelhalter DJ, Thomas A. Bayesian approaches to random-effects meta-analysis: a comparative study. Stat Med. 1995 Dec;14(24):2685–99.
66 Berlin JA. Invited commentary: benefits of heterogeneity in meta-analysis of data from epidemiologic studies. Am J Epidemiol. 1995 Aug;142(4):383–7.
67 Krassas GE, Poppe K, Glinoer D. Thyroid function and human reproductive health. Endocr Rev. 2010 Oct;31(5):702–55.
68 Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, et al.; American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid. 2011 Oct;21(10):1081–125.
69 Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid. 2017 Mar;27(3):315–89.
70 Pennington JA. A review of iodine toxicity reports. J Am Diet Assoc. 1990 Nov;90(11): 1571–81.
71 Taylor PN, Okosieme OE, Premawardhana L, Lazarus JH. Should all women be screened for thyroid dysfunction in pregnancy? Womens Health (Lond). 2015 Jun;11(3):295–307.
72 Lazarus JH, Bestwick JP, Channon S, Paradice R, Maina A, Rees R, et al. Antenatal thyroid screening and childhood cognitive function. N Engl J Med. 2012 Feb;366(6):493–501.
73 Casey BM, Thom EA, Peaceman AM, Varner MW, Sorokin Y, Hirtz DG, et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy. N Engl J Med. 2017 Mar;376(9):815–25.
74 Carlé A, Pedersen IB, Knudsen N, Perrild H, Ovesen L, Laurberg P. Hypothyroid symptoms and the likelihood of overt thyroid failure: a population-based case-control study. Eur J Endocrinol. 2014 Nov;171(5):593–602.
75 American Diabetes Association. Executive summary: Standards of medical care in diabetes – 2014. Diabetes Care. 2014 Jan;37 Suppl 1:S5–13.
76 Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, et al.; American Association Of Clinical Endocrinologists And American Thyroid Association Taskforce On Hypothyroidism In Adults. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid. 2012 Dec; 22(12):1200–35.
77 Stott DJ, Rodondi N, Kearney PM, Ford I, Westendorp RG, Mooijaart SP, et al.; TRUST Study Group. Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism. N Engl J Med. 2017 Jun;376(26):2534–44.
78 Tseng FY, Lin WY, Li CI, Li TC, Lin CC, Huang KC. Subclinical hypothyroidism is associated with increased risk for cancer mortality in adult Taiwanese – a 10 years population-based cohort. PLoS One. 2015 Apr; 10(4):e0122955.
79 Bano A, Chaker L, Plompen EP, Hofman A, Dehghan A, Franco OH, et al. Thyroid Function and the Risk of Nonalcoholic Fatty Liver Disease: the Rotterdam Study. J Clin Endocrinol Metab. 2016 Aug;101(8):3204–11.
80 Zhang Y, Chang Y, Ryu S, Cho J, Lee WY, Rhee EJ, et al. Thyroid hormone levels and incident chronic kidney disease in euthyroid individuals: the Kangbuk Samsung Health Study. Int J Epidemiol. 2014 Oct;43(5):1624–32.
81 Fleiner HF, Bjøro T, Midthjell K, Grill V, Åsvold BO. Prevalence of thyroid dysfunction in autoimmune and type 2 diabetes: the population-based HUNT study in Norway. J Clin Endocrinol Metab. 2016 Feb;101(2):669–77.