



# Subclinical hypothyroidism in paediatric population treated with levothyroxine: a real-world study on 2001–2014 Italian administrative data

Nella Augusta Greggio<sup>1</sup>, Elisa Rossi<sup>2</sup>, Silvia Calabria<sup>3</sup>, Alice Meneghin<sup>1</sup>,  
Joaquin Gutierrez de Rubalcava<sup>1</sup>, Carlo Piccinni<sup>3</sup> and Antonella Pedrini<sup>3</sup>

<sup>1</sup>Pediatric Endocrinology and Adolescence Unit, Department of Woman and Child Health, University of Padova, Padova, Italy

<sup>2</sup>CINECA – Interuniversity Consortium (Health Service), Bologna, Italy

<sup>3</sup>CORE srl – Collaborative Outcome Research, Bologna, Italy

Correspondence  
should be addressed  
to A Pedrini  
**Email**  
pedrini@coreteam.it

## Abstract

**Objective:** To estimate the prevalence of subclinical hypothyroidism (SH) among children, by using levothyroxine low dosage as disease proxy, and to describe prescription pattern.

**Design:** An historical cohort study was performed through administrative databases of 12 Italian Local Health Units covering 3,079,141 inhabitants. A cohort of children (aged 0–13 years) was selected in the period 2001–2014. A subgroup of new users (aged 0–9 years) was identified and followed up for 5 years.

**Methods:** The prevalence was provided as mean value of the whole period, as annual trend, by patient gender and age. Demographic details, information on levothyroxine dosage, comorbidities and co-medications were provided. Therapy duration and medication persistence were evaluated among new users.

**Results:** 644 children treated with levothyroxine low dosage was selected, with a mean annual prevalence of 0.20 per 1000 children. The temporal trend of prevalence was stable, with a slight reduction in the 2005–2008. Prevalence by age showed an increase after 10 years. Patients were treated with an average annual dose of 4290 µg/year and 66.9% of children were affected by comorbidities. Among 197 new users, 62.9% received therapy only for one year, whereas out of those treated two or more years, 89.0% resulted persistent to the therapy.

**Conclusions:** This study provides real-world epidemiology of SH among children, and it depicts the clinical and therapeutic characteristics of these subjects. Its findings showed that the SH treatment of this disorder was widely variable, also due to lack of evidence concerning paediatric population.

## Key Words

- ▶ subclinical hypothyroidism
- ▶ paediatric population
- ▶ prevalence
- ▶ levothyroxine
- ▶ real-world evidence

Endocrine Connections  
(2017) 6, 367–374

## Introduction

Subclinical hypothyroidism (SH) is a biochemical condition defined as serum thyroid-stimulating hormone (TSH) exceeding the limit of its reference range by age, while the concentration of serum free thyroxine (FT4) remains within its range. Signs and symptoms

of SH are absent; sometimes the slight symptoms of hypothyroidism are evident. The clinical significance of this mild hyperthyrotropynemia is uncertain; therefore, the debate about the appropriateness of treatment and diagnostic testing is still open. The prevalence of thyroid



dysfunctions among general population ranges from 1 to 10%, with higher estimates among women (up to 8 times rather than men) and elderly (1, 2). The National Health and Nutrition Examination Survey (NHANES III), the largest community-based study on thyroid function conducted in the United States, found that 4.6% of patients had hypothyroidism, out of these 4.3% was affected by a subclinical form of the disease (3). To date, data regarding the epidemiology of SH in children and pre-adolescents are scarce; however, the prevalence of SH in this population is estimated to be slightly lower than 2% (4).

SH can have autoimmune or non-autoimmune origins. It can be distinguished between congenital or acquired, and transient or permanent. Hypothyroidism diagnosis is based on a clinical suspicion confirmed by TSH titration that represents the most sensitive test available for this diagnosis. Thyroid function is systematically investigated during screening for congenital hypothyroidism in newborns, or in case of symptoms that are consistent with thyroid alterations, or also in case of additional visits for chronic conditions. It should be noticed that neonatal hyperthyrotropynemia can resolve spontaneously in some days or persist and therefore it requires a treatment (5). Hypothyroidism is considered at the earliest stages when TSH is above the age-specific reference value and FT4 is within normal limits. The current TSH reference values have been defined by the National Academy of Clinical Biochemistry (NACB) that has established the upper limit at 2.5  $\mu\text{U}/\text{mL}$  (6). According to these values, patients affected by SH could be divided into two groups: those with a slight increase of TSH (4.5–10  $\mu\text{U}/\text{mL}$ ) and those with a mild increase of TSH (>10  $\mu\text{U}/\text{mL}$ ). The risk of SH progression to overt hypothyroidism is less common in paediatric population and adolescents than that in adults (<1–20%) (4, 7). Usually, children show a natural decrease in TSH up to euthyroidism or no change in the condition of SH (8, 9). Treatment of SH is a controversial theme in adult patients and even more in children where there are very few studies comparing treated vs non-treated children (10, 11, 12, 13, 14, 15, 16, 17). For this reason, the available European guidelines are not definitive on treatment of this population: it generally recommends a treatment with levothyroxine in children aged <3 years, in order to support the thyroid hormone effects on brain maturation (18). In addition, the American guidelines suggest treating children with signs and symptoms of thyroid dysfunction and at major risk of overt hypothyroidism also, especially when TSH is over 10  $\mu\text{U}/\text{mL}$ . Nevertheless, US general

practitioners and paediatric endocrinologists tend to prescribe levothyroxine more to prevent than to cure this condition (19). This attitude could be due to the well-known clinical consequences of a non-treated SH in adults (i.e. increased risk of cardiovascular diseases, depression, lipid disorders, high serum prolactin concentration and negative impact on the haemostatic profile) (20, 21, 22, 23, 24, 25). In particular, specific researches on cardiovascular risk among children with untreated SH showed some metabolic abnormalities (pro-atherogenic abnormalities) in these subjects, suggesting a close monitoring of all cardiovascular risk factors in this patient group (26, 27). While transposing these benefits in the paediatric population, the fact remains that the adverse effects of therapy with levothyroxine in this special population are not known (28, 29).

In this scenario, it becomes essential to provide real-world evidence on SH in paediatric population. Therefore, this study is aimed to estimate the prevalence of SH among children (aged 0–13 years) using a low dosage of levothyroxine as disease proxy. Moreover, the study describes the characteristics of subject affected by SH and the prescription pattern of levothyroxine in terms of dosage, persistence and therapy duration.

## Methods

### Data source

This historical cohort study was performed using data of CINECA ARNO Observatory, a population-based Italian database (30). Since 1987, the CINECA ARNO Observatory routinely collects and integrates National Health System (NHS) administrative data for each single patient (i.e. patient demographics, reimbursed drug prescriptions, inpatient hospital discharges, invasive/non-invasive specialist/diagnostic procedures). For each reimbursed drug prescription, the following information were collected: the specific medicinal product (with the relevant dosage), the active substance coded by using the Anatomical Therapeutic Chemical classification (ATC), the number of dispensed packages, the dispensing date and the cost of the product and of the relevant generic (31). Demographic information was made anonymous, according to Italian law regarding the protection of privacy (32). This study does not require ethical approval since it is based on the collection of anonymous administrative data, and it is conducted for institutional purposes, by

means of a specific agreement with Italian National Health Facilities (Regions and LHUs).

At 2014, CINECA ARNO Observatory included data of 32 Italian LHUs, covering a population of over 11 million of citizens.

### Cohort selection

This study was performed on a subset of ARNO database including 12 Italian LHUs (covering 3,079,141 inhabitants) with complete information in the period 2001–2014. Starting from this population were identified children aged 0–13 years in the period 2001–2014. The amount of paediatric population investigated varied in each year with an average annual amount of 395,737 children (min 380,308 in 2004, max 422,378 in 2013). Within this population, the cohort of children affected by SH was selected. A child was considered to be affected by SH if he/she received a 'low dosage' levothyroxine (ATC code: H03AA01) from January 1st to December 31st 2004 (33, 34).

The 'low dosage' was defined according to the children's age, by setting the following thresholds:

1.  $\leq 7000 \mu\text{g}/\text{year}$  for children in the first year of life, by considering a upper limit of daily dosage of  $18.75 \mu\text{g}/\text{die}$
2.  $\leq 9000 \mu\text{g}/\text{year}$  for children between 2 and 3 years old, by considering a upper limit of daily dosage of  $25.00 \mu\text{g}/\text{die}$
3.  $\leq 13,700 \mu\text{g}/\text{year}$  for children over 3 years old, by considering a upper limit of daily dosage of  $37.50 \mu\text{g}/\text{die}$

The annual total amount of levothyroxine was calculated by summing the doses of 25, 50 and  $75 \mu\text{g}$  dispensed in a year for each subject.

In order to select patients with a SH diagnosis, the children affected by congenital or severe acquired hypothyroidism (disease exemption code 027) and those affected by Hashimoto's thyroiditis (disease exemption code 048) or malignant tumour (disease exemption code 056) were excluded from this cohort. The last two cases were excluded because of the likely development of overt thyroiditis, which cannot be easily distinguished from the subclinical form through administrative data. The exclusions from the study cohort were carried out by using the presence of specific exemption codes in health administrative databases as reliable proxies of the above listed diseases. The first prescription of levothyroxine retrieved in the study period was considered as the index

date for each child. Selected patients were observed from the index date until 31st December, 2014, or the 14th birthday (excluded).

### Prevalence estimation, patient characteristics and prescription patterns

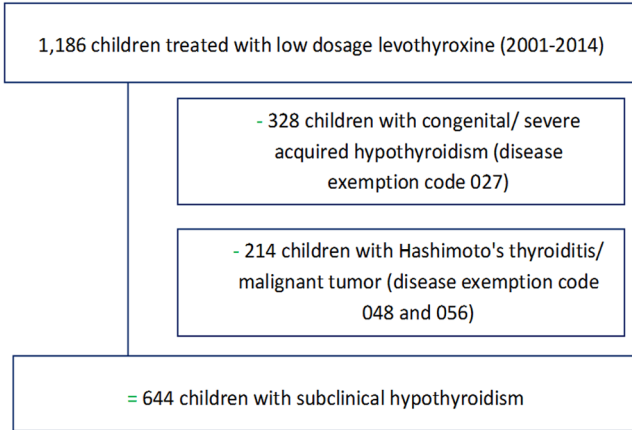
The prevalence of SH was estimated by dividing the number of subjects addressing the inclusion and exclusion criteria, as defined above, in each year, with the paediatric population (0–13 years old) in the same year. The prevalence was expressed  $\times 1000$  children per year.

For each prevalent subject, demographic details, information on levothyroxine dosage, comorbidities and co-medications were provided. Among demographic characteristics were considered age, gender and country of birth. The levothyroxine dosage was expressed as mean yearly dose received by subject in the study period, and it was described for different patient ages. Comorbidities were assessed through the presence in the database of disease exemption codes and prescription of drugs for chronic conditions throughout the whole study period. The levothyroxine prescription pattern, in terms of therapy duration and medication persistence, was evaluated only for new users in the period 2004–2014. A subject was considered new user when no prescription of levothyroxine was retrieved in the 3 years before the index date. Therapy duration was expressed as years in treatment, through the difference between the year of first prescription and the year of last prescription. For those patients with at least 2 years of treatment was assessed the medication persistence over a 5-year follow-up. A patient was considered persistent when there is no gap of 1 year. It was found in the prescription history, according the persistence definition of the International Society for Pharmacoeconomics and Outcome Research (ISPOR) (35). Conversely, a patient was defined with a discontinued therapy when there was an interruption of therapy in one or more years and then a restarting of therapy.

Apposite statistical tests were used to assess any significant difference ( $P$  value  $< 0.05$ ) between males and females: Chi-square test, Mann–Whitney  $U$  test and independent two-sample  $t$ -test.

### Results

Over the 14-year accrual period (2001–2014a), cohort of 1186 children (0–13 years old) treated with low dosage of

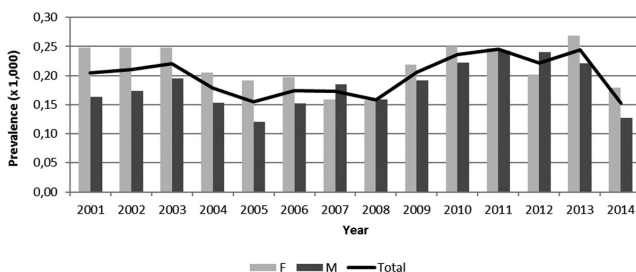


**Figure 1**  
Cohort selection.

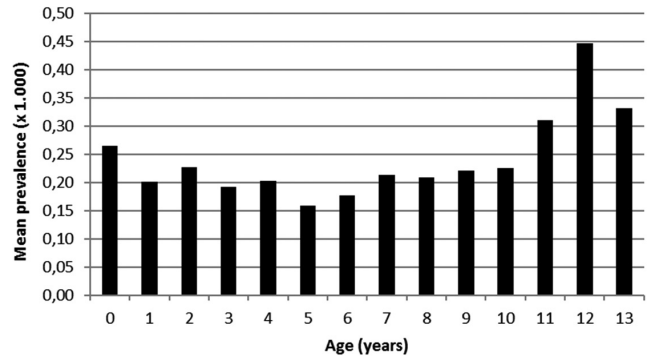
levothyroxine was selected, of which 328 had congenital/severe acquired hypothyroidism and 214 Hashimoto's thyroiditis or history of malignant tumour. Therefore, 644 children represented the final cohort (Fig. 1). Out of these, 52.8% (340 subjects) was females, with a mean age of 7.4 years. By country of birth, 95.7% (616) was Italian, 2.6% (17) was from other European countries and 1.7% (11) from Non-European countries (i.e. South America, Asia, Africa, People's Republic of China and USA).

In the period 2001–2014, the mean annual prevalence of treated SH in the paediatric population was 0.20 per 1000 children. It was higher in females than that in males (0.22 vs 0.18 per 1000). The temporal trend of SH prevalence was almost stable, with a slight reduction in the 2005–2008 period. Furthermore, the prevalence was higher for females than that in males in all considered years, with the exception of 2007 and 2012 (Fig. 2).

Prevalence of SH by patient age showed that after a value of 0.26 per 1000 among patients with less than 1 year, it steadied in children between 1 and 10 years (range 0.18–0.22 per 1000), whereas it increased in the



**Figure 2**  
Prevalence of treated SH among paediatric population (0–13 years old) from 2001 to 2014, stratified by gender.

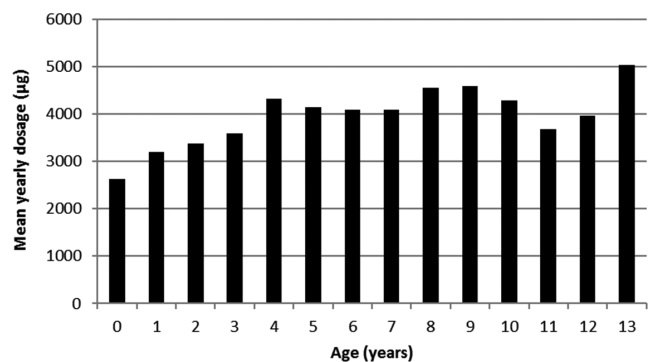


**Figure 3**  
Prevalence of treated SH in the paediatric population (0–13 years old) from 2001 to 2014, stratified by age.

subsequent ages reaching a peak among subjects with 12 years (0.45 per 1000) (Fig. 3).

Concerning the levothyroxine dosage used in this cohort of subjects, the analysis showed that patients were treated with an average annual dose of 4290 µg/year (min. 1250–max. 12,500 µg/year; standard deviation (s.d.) 2403 µg/year), without any significant difference between genders. The analysis of dosages by patient age underlined that there was an increase of average annual dose from 0 year (2634 µg/year) to 4 years (4323 µg/year); in the subsequent age, the used dose steadied around 4000 µg/year and reached a peak in the 13th year (5041 µg/year) (Fig. 4).

Analysis of comorbidities showed that 66.9% of children with treated SH had at least another disease. The most frequent comorbidities were disability (12.4%), rare disease (10.6%), cardiovascular disease (8.5%), prematurity/immaturity (7.6%) and severe congenital physical/sensory/neurological deficits (4.7%). Moreover, 2.3% of our cohort had diabetes, 2.3% Down syndrome, 1.1% celiac disease, and 0.6% Turner syndrome. In the



**Figure 4**  
Mean dosage (µg/year) dispensed to paediatric population (0–13 years old) from 2001 to 2014, stratified by age.

**Table 1** Duration and medication persistence of levothyroxine therapy among new users aged 0–9 years old.

Therapy duration (year)	N (% of new users)	Persistent	Not persistent
		N (% of each duration group)	N (% of each duration group)
≤1	124 (62.9)	–	–
>1	73 (37.1)	65 (89.0)	8 (11.0)
2	18 (9.1)	16 (88.9)	2 (11.1)
3	18 (9.1)	15 (83.3)	3 (16.7)
4	15 (7.6)	12 (80.0)	3 (20.0)
5	22 (11.2)	22 (100)	0 (0.0)

cohort of children with treated SH, the most prescribed co-medications were antibacterials for systemic use (92.5%), antiasthmatics (71.4%), corticosteroids (39.4%) and antihistamines (30.3%) for systemic use. The most prescribed co-medications among children affected by SH are the same of those prescribed to the Italian general children population, as reported in the official Italian report on medicine utilisation (36).

Medication persistence was assessed on the sub-cohort of levothyroxine new users aged 0–9 years consisting of 197 children (48.2% females) that started levothyroxine therapy between 2004 and 2010 and were followed up for 5 years. Most of them (62.9%) received specific therapy only for one year. Out of 73 patients who received levothyroxine for more than one year, 89.0% (65 subjects) was persistent and 11.0% (8 subjects) was not persistent (Table 1). Within not persistent patients, 7 have discontinued the treatment one time and 1 two times. Mean duration of therapy interruption was  $1.13 \pm 0.354$  years. No significant difference between genders was found.

## Discussion

SH in the paediatric population is still widely debated. Literature affirms that SH is a transient condition and that pharmacological treatment does not modify its evolution (4, 13). Nowadays, guidelines concerning therapeutic approach, dosage or type of patient to treat, do not exist. Moreover, the studies reporting the epidemiology of SH in children and adolescents are scarce. This study tries to fill this gap of information by providing estimation of SH prevalence among Italian children and pre-adolescents (0–13 years). The study, by searching Italian administrative databases, found that the prevalence of treated SH was 0.20 per 1000 children, in the period 2001–2014. By analysing the temporal trend of the prevalence, some fluctuations

have emerged. This phenomenon can be due to both real fluctuations over the follow-up period and to different therapeutic approaches. In fact, very few and opposing studies give indications on pharmacological treatment of SH in paediatric population (4, 37, 38).

A slight change in the thyroid function can happen at any age: in the first years of life, it could be due to thyroid dysgenesis and genetic causes, while at older ages iodine deficit, chronic diseases and obesity are more frequent aetiologies of thyroid function changes. Therefore, it becomes crucial to study the prevalence of treated SH according to the patient age. Our analysis showed that the prevalence by age, after a high value in the first year life, resulted almost homogeneous between 1 and 10 years, finally it increased from 11 to 13 years. Therefore, even if the SH treatment can be started at any age, our study found that it is more frequently instituted in early childhood and among pre-adolescent patients (11–13 years). Evidence from literature displayed that TSH is usually screened after the age of 8 years with a peak at the pre-adolescent/adolescent stage (12–16 years); probably because of pubertal delay symptoms, problems and indolence at school, overweight or obesity (39).

Recently, two studies showed that TSH is higher in obese children compared to ones with normal weights (28, 29). Nevertheless, treatment of obese patients with SH is an inappropriate clinical attitude, because it has been demonstrated that with weight-loss TSH gradually decreases to a normal range (40). Our findings showed that mean dosages prescribed were uniform in different age groups. This is consistent with the fact that levothyroxine is not titrated according to the child's weight, as it happens in overt hypothyroidism, because very low dosages are sufficient to normalise TSH.

In the same line of other studies, our analysis confirmed the association between SH and prematurity and with some chronic diseases. In fact, SH can be due to Hashimoto's thyroiditis, because of a greater predisposition to autoimmunity or other events that alter the thyroid function (41).

With regard to medication persistence, this study found that the preferred therapeutic approach is to treat children with SH for short periods, one year or less, until TSH normalises. This seems to confirm the literature definition of SH as a mostly transient condition (4). In fact, SH can last from a few months to some years, or a lifetime, in case of genetic forms (42). In any event, this treatment seems to be, instead, a therapeutic attempt that is often chosen in case of haematologic tests with high TSH value. However, such a short therapy seems

unable either to modify the natural course of SH in patients with TSH between 5 and 10  $\mu\text{U}/\text{mL}$  in case of hyperthyrotropynemia, nor to prevent the risk of a further TSH increase after discontinuation (13). Nevertheless, it is crucial to notice that the choice to start a levothyroxine therapy should be based on the analysis of the overall context including symptoms, TSH values and relevant comorbidities. Moreover, the main goal of this therapy should have the intent to solve symptoms and signs related to the disease. However, a significant clinical improvement due to treatment has been pointed out in children with chronic comorbidities (diabetes, physical deficits or Down syndrome) (10, 11, 12, 13, 14, 43). Therefore, as 66.9% of identified SH patients was affected by another chronic disease, it is possible to consider most of retrieved treatment appropriate.

Limitations of this analysis must be listed as well. First the prevalence estimations, provided in this study, referred to children in treatment with levothyroxine and not to the actual population suffering from SH. Therefore, our estimations could underestimated the actual epidemiology of this condition. However, our analysis identified only patients treated with 'low dosage' of levothyroxine and therefore potentially affected by SH, indeed, we excluded those subjects affected by overt hypothyroidism, which would need higher dosages. Other limitations were because our study was performed on routinely and previously collected administrative data, so it was affected by the typical weaknesses of the retrospective designs. In particular, administrative data did not collect information on values emerging from the laboratory test examinations; therefore, our study was unable to distinguish between patients with TSH  $>10\mu\text{U}/\text{mL}$ , where guidelines suggest to start a pharmacological treatment and those with TSH 5–10  $\mu\text{U}/\text{mL}$ . Regardless, literature provides evidence that adult patients with TSH between of 5 and 10  $\mu\text{U}/\text{mL}$  are 74% of all patients with SH, while those with TSH  $>10\mu\text{U}/\text{mL}$  are 26% (44). Since there are no data relating to TSH value in children, it could be supposed the same distribution in the paediatric population. Moreover, due to unavailability of the database collecting TSH investigation requests for the entire study period, it has not been possible to use this information as a proxy of unstable disease. An additional drawback was related to the missing information of the specific daily dosage in administrative databases. However, these data can be derived from the analysis of the whole prescription history for a given subject. In addition, data on weight, height, subjects' attitudes and diet are missing in this kind of data sources; therefore,

our analysis could be affected by limitations linked to these aspects.

## Conclusions

This is the first study that provides epidemiological data about SH in children and pre-adolescents, 0–13 years. The only data available are referred to a population aged 13–16 years (45). Specifically, we identified the paediatric population with SH that has been treated with hormone replacement therapy. In fact, since SH is often asymptomatic, it is not always treated. This study is therefore a starting point for further analyses to provide more information on the logic of the therapeutic approach, by clarifying the real levothyroxine monthly/daily consumption, by linking administrative databases with laboratory and clinical ones, and by determining the appropriateness of the treatment. Evidence produced with this analysis provide an important picture of the Italian clinical approach considering the non-existent literature on children and pre-adolescents with treated SH.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

### Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector

### References

- Vanderpump M & Tunbridge W. The epidemiology of thyroid diseases. In *The Thyroid: A Fundamental and Clinical Text*, 8th ed, pp 467. Eds L Braverman & R Utiger. Philadelphia, PA, USA: Lippincott Williams & Wilkins, 2000.
- Institute of Medicine (US) Committee on Medicare Coverage of Routine Thyroid Screening. Eds M Stone & R Wallace. Washington DC, USA: National Academies Press (US), 2003.
- Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE & Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 489–499. (doi:10.1210/jcem.87.2.8182)
- Monzani A, Prodam F, Rapa A, Moia S, Agarla V, Bellone S & Bona G. Endocrine disorders in childhood and adolescence. Natural history of subclinical hypothyroidism in children and adolescents and potential effects of replacement therapy: a review. *European Journal of Endocrinology* 2012 **168** R1–R11. (doi:10.1530/EJE-12-0656)
- Boscherini B, Fonte M & Dal Balzo P. In *Endocrinologia nella pratica pediatrica*. Padova, Italy: Piccin, 2013.
- Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruf J, *et al.* Laboratory

- medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid* 2003 **13** 3–126. (doi:10.1089/10507250321086962)
- 7 Moore DC. Natural course of 'subclinical' hypothyroidism in childhood and adolescence. *Archives of Pediatrics and Adolescent Medicine* 1996 **150** 293–297. (doi:10.1001/archpedi.1996.02170280063012)
  - 8 Wasniewska M, Salerno M, Cassio A, Corrias A, Aversa T, Zirilli G, Capalbo D, Bal M, Mussa A & De LF. Prospective evaluation of the natural course of idiopathic subclinical hypothyroidism in childhood and adolescence. *European Journal of Endocrinology* 2009 **160** 417–421. (doi:10.1530/EJE-08-0625)
  - 9 Gopalakrishnan S, Chugh PK, Chhillar M, Ambardar VK, Sahoo M & Sankar R. Goitrous autoimmune thyroiditis in a pediatric population: a longitudinal study. *Pediatrics* 2008 **122** e670–e674. (doi:10.1542/peds.2008-0493)
  - 10 Cetinkaya E, Aslan A, Vidinlisan S & Ocal G. Height improvement by L-thyroxine treatment in subclinical hypothyroidism. *Pediatrics International* 2003 **45** 534–537. (doi:10.1046/j.1442-200X.2003.01786.x)
  - 11 Chase HP, Garg SK, Cockerham RS, Wilcox WD & Walravens PA. Thyroid hormone replacement and growth of children with subclinical hypothyroidism and diabetes. *Diabetic Medicine* 1990 **7** 299–303. (doi:10.1111/j.1464-5491.1990.tb01393.x)
  - 12 Eyal O, Blum S, Mueller R, Smith FO & Rose SR. Improved growth velocity during thyroid hormone therapy in children with Fanconi anemia and borderline thyroid function. *Pediatric Blood and Cancer* 2008 **51** 652–656. (doi:10.1002/pbc.21673)
  - 13 Wasniewska M, Corrias A, Aversa T, Valenzise M, Mussa A, De ML, Lombardo F, De LF & Salerno M. Comparative evaluation of therapy with L-thyroxine versus no treatment in children with idiopathic and mild subclinical hypothyroidism. *Hormone Research in Paediatrics* 2012 **77** 376–381. (doi:10.1159/000339156)
  - 14 Mohn A, Di MS, Di LR, Tumini S & Chiarelli F. The effect of subclinical hypothyroidism on metabolic control in children and adolescents with Type 1 diabetes mellitus. *Diabetic Medicine* 2002 **19** 70–73. (doi:10.1046/j.1464-5491.2002.00635.x)
  - 15 Svensson J, Ericsson UB, Nilsson P, Olsson C, Jonsson B, Lindberg B & Ivarsson SA. Levothyroxine treatment reduces thyroid size in children and adolescents with chronic autoimmune thyroiditis. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 1729–1734. (doi:10.1210/jc.2005-2400)
  - 16 Rother KI, Zimmerman D & Schwenk WF. Effect of thyroid hormone treatment on thyromegaly in children and adolescents with Hashimoto disease. *Journal of Pediatrics* 1994 **124** 599–601. (doi:10.1016/S0022-3476(05)83141-5)
  - 17 Aijaz NJ, Flaherty EM, Preston T, Bracken SS, Lane AH & Wilson TA. Neurocognitive function in children with compensated hypothyroidism: lack of short term effects on or off thyroxin. *BMC Endocrine Disorders* 2006 **20** 2. (doi:10.1186/1472-6823-6-2)
  - 18 Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R & Vaidya B. European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. *European Thyroid Journal* 2014 **3** 76–94. (doi:10.1159/000362597)
  - 19 Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, Cooper DS, Kim BW, Peeters RP, Rosenthal MS, et al. Guidelines for the treatment of hypothyroidism: prepared by the American thyroid association task force on thyroid hormone replacement. *Thyroid* 2014 **24** 1670–1751. (doi:10.1089/thy.2014.0028)
  - 20 Althaus BU, Staub JJ, Ryff-De LA, Oberhansli A & Stahelin HB. LDL/HDL-changes in subclinical hypothyroidism: possible risk factors for coronary heart disease. *Clinical Endocrinology* 1988 **28** 157–163. (doi:10.1111/j.1365-2265.1988.tb03651.x)
  - 21 Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A & Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. *Annals of Internal Medicine* 2000 **132** 270–278. (doi:10.7326/0003-4819-132-4-200002150-00004)
  - 22 Demartini B, Ranieri R, Masu A, Selle V, Scarone S & Gambini O. Depressive symptoms and major depressive disorder in patients affected by subclinical hypothyroidism: a cross-sectional study. *Journal of Nervous and Mental Disease* 2014 **202** 603–607. (doi:10.1097/NMD.0000000000000168)
  - 23 Suh S & Kim DK. Subclinical hypothyroidism and cardiovascular disease. *Endocrinology and Metabolism* 2015 **30** 246–251. (doi:10.3803/EnM.2015.30.3.246)
  - 24 Staub JJ, Althaus BU, Engler H, Ryff AS, Trabucco P, Marquardt K, Burckhardt D, Girard J & Weintraub BD. Spectrum of subclinical and overt hypothyroidism: effect on thyrotropin, prolactin, and thyroid reserve, and metabolic impact on peripheral target tissues. *American Journal of Medicine* 1992 **92** 631–642. (doi:10.1016/0002-9343(92)90782-7)
  - 25 Muller B, Tsakiris DA, Roth CB, Guglielmetti M, Staub JJ & Marbet GA. Haemostatic profile in hypothyroidism as potential risk factor for vascular or thrombotic disease. *European Journal of Clinical Investigation* 2001 **31** 131–137. (doi:10.1046/j.1365-2362.2001.00777.x)
  - 26 Cerbone M, Capalbo D, Wasniewska M, Mattace RG, Alfano S, Meli R, De LF & Salerno M. Cardiovascular risk factors in children with long-standing untreated idiopathic subclinical hypothyroidism. *Journal of Clinical Endocrinology and Metabolism* 2014 **99** 2697–2703. (doi:10.1210/jc.2014-1761)
  - 27 Cerbone M, Capalbo D, Wasniewska M, Alfano S, Mattace RG, Oliviero U, Cittadini A, De LF & Salerno M. Effects of L-thyroxine treatment on early markers of atherosclerotic disease in children with subclinical hypothyroidism. *European Journal of Endocrinology* 2016 **175** 11–19. (doi:10.1530/EJE-15-0833)
  - 28 Such K, Gawlik A, Dejner A, Wasniewska M, Zachurzok A, Antosz A, Gawlik T & Malecka-Tendera E. Evaluation of subclinical hypothyroidism in children and adolescents: a single-center study. *International Journal of Endocrinology* 2016 **2016** 1671820. (doi:10.1530/EJE-15-0833)
  - 29 Wasniewska M, Aversa T, Salerno M, Corrias A, Messina MF, Mussa A, Capalbo D, De LF & Valenzise M. Five-year prospective evaluation of thyroid function in girls with subclinical mild hypothyroidism of different etiology. *European Journal of Endocrinology* 2015 **173** 801–808. (doi:10.1530/EJE-15-0484)
  - 30 CINECA. ARNO observatory 2017. (available at: <http://arno.cineca.it/portal/>).
  - 31 WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD methodology 2017. (available at: <https://www.whocc.no/>).
  - 32 Italian Data Protection Authority. Authorisation no. 9/2014 – General Authorisation to Process Personal Data for Scientific Research Purposes [3786078] 2014. (available at: <http://www.garantepivacy.it/web/guest/home/docweb/-/docweb-display/docweb/3786078>)
  - 33 Corsello S. Endocrinologia (Endocrinology). In *Manuale di Terapia Medico-chirurgica (Manual of Medical and Surgical Therapy)*. Ed Gui. Rome, Italy: CIC Edizioni Internazionali, 2004.
  - 34 Corsello SM, Migneco MG & Lovicu RM. Medical therapy of benign thyroid diseases. *Rays* 1999 **24** 315–330.
  - 35 Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA & Wong PK. Medication compliance and persistence: terminology and definitions. *Value Health* 2008 **11** 44–47. (doi:10.1111/j.1524-4733.2007.00213.x)
  - 36 Italian Medicines Agency. The medicines utilisation monitoring centre. National report on medicines use in Italy 2015, 2016. (available at: [http://www.aifa.gov.it/sites/default/files/OsMed\\_2015\\_Eng.pdf](http://www.aifa.gov.it/sites/default/files/OsMed_2015_Eng.pdf))
  - 37 Salerno M, Capalbo D, Cerbone M & De LF. Subclinical hypothyroidism in childhood – current knowledge and open

- issues. *Nature Reviews Endocrinology* 2016 **12** 734–746. (doi:10.1038/nrendo.2016.100)
- 38 Catli G, Abaci A, Buyukgebiz A & Bober E. Subclinical hypothyroidism in childhood and adolescence. *Journal of Pediatric Endocrinology and Metabolism* 2014 **27** 1049–1057.
- 39 Lazar L, Frumkin RB, Battat E, Lebenthal Y, Phillip M & Meyerovitch J. Natural history of thyroid function tests over 5 years in a large pediatric cohort. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 1678–1682. (doi:10.1210/jc.2008-2615)
- 40 Reinehr T & de SG Andler W. Hyperthyrotropinemia in obese children is reversible after weight loss and is not related to lipids. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 3088–3091. (doi:10.1210/jc.2006-0095)
- 41 Sharav T, Landau H, Zadik Z & Einarson TR. Age-related patterns of thyroid-stimulating hormone response to thyrotropin-releasing hormone stimulation in Down syndrome. *American Journal of Diseases of Children* 1991 **145** 172–175. (doi:10.1001/archpedi.1991.02160020064018)
- 42 Nicoletti A, Bal M, De MG, Baldazzi L, Agretti P, Menabo S, Ballarini E, Cicognani A, Tonacchera M & Cassio A. Thyrotropin-stimulating hormone receptor gene analysis in pediatric patients with non-autoimmune subclinical hypothyroidism. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 4187–4194. (doi:10.1210/jc.2009-0618)
- 43 van Trotsenburg AS, Vulmsa T, van Rozenburg-Marres SL, van Baar AL, Ridder JC, Heymans HS, Tijssen JG & de Vijlder JJ. The effect of thyroxine treatment started in the neonatal period on development and growth of two-year-old Down syndrome children: a randomized clinical trial. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 3304–3311. (doi:10.1210/jc.2005-0130)
- 44 Garg A & Vanderpump MP. Subclinical thyroid disease. *British Medical Bulletin* 2013 **107** 101–116. (doi:10.1093/bmb/ldt024)
- 45 Wu T, Flowers JW, Tudiver F, Wilson JL & Punyasavatsut N. Subclinical thyroid disorders and cognitive performance among adolescents in the United States. *BMC Pediatrics* 2006 **19** 6–12.

---

Received in final form 12 June 2017

Accepted 14 June 2017

Accepted Preprint published online 14 June 2017

