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**Lauri J Virta · Seija I Eskelinen**

L. Virta

The Social Insurance Institution, Research Department,  
Turku, Finland

S. Eskelinen

Pori Health Center, Pori, Finland

Address for corresponding:

Department of Family Medicine, University of Turku

Lemminkäisenkatu 1

20014 Turku, Finland

e-mail seiesk@utu.fi

Tel: +358 40072275

Fax: +358 23338439

## Abstract

*Purpose* The aim of this study was to estimate the one-year prevalence of levothyroxine-treated hypothyroidism in Finland.

*Methods* From the nationwide Finnish Drug Prescription Database we retrieved all individuals who had regularly purchased the levothyroxine medication during the year 2007. The prevalence rates and 95% CIs were calculated per 100 persons assuming a Poisson distribution.

*Results* Altogether, 189,027 persons (female 84%) used levothyroxine tablets and, hence, the one-year prevalence of hypothyroidism was 3.6%. The disease was notably more common in females (5.9%) than in males (1.2%); the gender prevalence rate ratio (PRR) was 4.5. Prevalence increased with age. Regionally, between five university hospitals districts the prevalence rates were fairly stable, the lowest rate was 3.1% and the highest 4.4%, regional PRR was 1.3.

*Conclusions* To the best of our knowledge, this nationwide prescription study deals with the largest population of reported levothyroxine users to date. This comprehensive data justifies estimating the gender- and age-specific prevalence of hypothyroidism in Finland.

**Keywords** Drug therapy • Finland • Hypothyroidism • Levothyroxine treatment • Pharmacoepidemiology • Prevalence • Registries

**Introduction**

Hypothyroidism is the most common pathological hormone deficiency, and levothyroxine is the treatment of choice. In patients with primary hypothyroidism dysfunction is in the level of thyroid gland and serum thyrotropin (TSH) is elevated. In patients with central, also secondary hypothyroidism, the TSH level is low or low-normal [1]. Controversy [2] in the diagnosis and treatment of subclinical (biochemical) hypothyroidism, defined as mildly elevated TSH with normal free thyroid hormone values and questionable symptoms, may affect the prevalence rates of hypothyroidism nationally or even regionally.

Because primary hypothyroidism is much more frequent (95%) than secondary hypothyroidism (5%), the concentration of TSH above the normal range has been used to estimate the prevalence of hypothyroidism in the United States, resulting in prevalence rates ranging from 4.6% (0.3% clinical and 4.3% subclinical) [3] to 9.5% (0.4% clinical and 9.0% subclinical) [4]. However, conclusions based on a single laboratory measurement are a well-known problem and the TSH measurement should be carried out in the morning, which decreases the participation rate. Some of the studies on the prevalence of hypothyroidism are based on estimates from diverse clinical populations or questionnaires with uncertain self-reported diseases.

There are no previous studies on the prevalence of hypothyroidism in Finland. In other Nordic Countries, the prevalence of hypothyroidism has been studied mostly in select age groups in one or a few geographical regions. The only large population-based study from Norway [5] showed that the prevalence of former diagnosed hypothyroidism was 4.8% in females and 0.9% in males.

The purpose of this study was to estimate the one-year prevalence of hypothyroidism in Finland according to regular purchases of levothyroxine by analyzing data from a comprehensive nationwide Prescription Database. We also wanted to study if there are regional differences in levothyroxine use between university hospital districts.

### **Patients and methods**

Finland has a National Health Insurance Scheme, which covers all residents living in a particular community, and a unique personal social security number is used as identification for each insured person. This code reveals their birth date and gender. The expenses of medicinal products prescribed by a physician for treatment of an illness are partially (42% or 72%) or totally (100%) reimbursed by the Social Insurance Institution (SII) of Finland [6].

Outside institutions, the treatment of hypothyroidism with levothyroxine sodium tablets (0.1 mg or 25 µg) is available by prescription only. The prescriptions are valid for one year from the day on which they were prescribed, but Finnish reimbursement regulations restrict the maximum number of tablets supplied per redemption to cover only a three-month period. Therefore, patients with chronic conditions and in need of daily drug treatment, such as hypothyroidism, generally redeem prescriptions several times (at least 3 discrete purchasing days) during a year, and we considered those patients to be persistent levothyroxine users.

### *Data source and collection*

All drugs prescribed by physicians to outpatients and reimbursed by the National Health Insurance Scheme are registered in a Finnish Drug Prescription Register,

established in 1993 and maintained by SII [7]. For defining pharmaceuticals, the Anatomical Therapeutic Chemical (ATC) classification system is used [8]. The register also contains the dispensing date for the prescription, the number of dispensed packages and tablets and information on the person's place of residence.

Previously, before the year 2006, a remarkable number of levothyroxine purchases were not reimbursed and, thus, not registered because of the low price of the drug (less than 10 Euros per package of 100 levothyroxine tablets). When, at the beginning of 2006, the method of calculating reimbursement payments in the Finnish insurance system changed, it appeared to be an exceptional opportunity for estimating the prevalence of the hypothyroid disease within the general population. With the reform, the fixed non-reimbursable sum paid by the patient per purchase (10 Euros) was abandoned. In the new system, the reimbursement payment is calculated separately for each medical product, and thereby almost every levothyroxine purchase is visible in the drug prescription register. According to the wholesale statistics of the National Agency for Medicines (NAM), in 2007 the prescription register covered 95.7% of total levothyroxine sodium consumption (in DDDs) in Finnish outpatient care (Tinna Voipio, NAM, personal communication).

From the nationwide drug prescription register, we retrieved all individuals who, from 1 January 2006 to 31 December 2008, purchased medicines belonging to ATC-code H03AA01. In 2007, altogether 192,927 outpatients redeemed at least one prescription of levothyroxine. The final study data here consists of those patients who redeemed their levothyroxine prescriptions during at least 3 discrete days; either during the year 2007 or by also making their purchases in the years 2006 and/or 2008.

The prevalence rates of hypothyroidism were calculated by dividing the number of patients purchasing levothyroxine in the year 2007 as nominator by the population at risk (per 100 persons) as denominator. The group at risk consisted of the whole Finnish population at the end of 2007 (5.30 million) [9] – excluding 24,810 persons residing year-round (2007) in a public nursing home or hospital [10].

### *Statistics*

The 95% confidence intervals (95% CI) for the prevalence rates were calculated assuming a Poisson distribution. A Poisson regression model was used to adjust the rates for gender or age (categorized as 0–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79 and >79 years). Comparisons were further made between the five university hospital districts in Finland (Table 2). The statistical significance of the relationships of prevalent cases based on gender or area was quantified by calculating the prevalence rate ratio (PRR) with a 95% CI. P-values less than 0.05 were considered to be statistically significant. Statistical computation was performed using the GENMOD procedure in the SAS system for Windows, version 9.1/2004.

### *Ethical considerations*

Ethical approval was not necessary, since we analysed only encrypted register data and did not contact the unidentifiable study subjects.

### **Results**



In the year 2007, altogether 189,027 outpatients (female 84%) regularly used levothyroxine in Finland. This places the nationwide prevalence of drug-treated hypothyroidism at 3.6% (95 % CI: 3.57 to 3.60). The disease was notably more common in females (5.9%) than in males (1.2%) (Table 1); the gender PRR was 4.5 (95 % CI: 4.48–4.59),  $p<0.001$ , after adjusting for age.

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The mean age of stable thyroxine users was 61.3 (SD 16.3) years; 43% of the patients were older than 64 years and 56% were at working age (16–64 years). The highest prevalence rate, 11.0%, was seen in the oldest age group (over 79 years), and the prevalence rate peaked in males at the age of 98 years (9.4%) and in females at the age of 75 years (14.2%). Within all age groups, the prevalence rates differed significantly between gender, the difference was greatest in the age group 30–39 (Table 1).

Regional prevalence figures varied slightly (Table 2). The highest prevalence rate (4.4%) was seen in the university hospital district of Turku and the lowest (3.1%) in the Helsinki district (the district adjacent to Turku); the regional PRR was 1.3 (95% CI: 1.25–1.29),  $p<0.001$ , after adjusting for age and gender. In the southern and western parts of Finland (the districts of Helsinki, Turku and Tampere) the prevalence rate was 3.5%, whereas in the eastern and northern parts of Finland (the districts of Kuopio and Oulu) it was 3.8%; this regional PRR was only barely significant, 1.06 (95% CI: 1.05–1.07),  $p<0.001$ , after adjusting for age and gender.

Table 2 here

The median daily consumption of levothyroxine was 92.3 µg (mean 92.6 + 40.0 µg per day; 103.1 in males and 90.5 in females). The mean daily dosages were associated with the patients' age (Figure 1). There were 26,219 (13.9%) patients with a low daily dose of levothyroxine (less than 51 µg) and 15,971 (8.4%) patients with a high daily dose (more than 150 µg). In the former subgroup the mean age was 64.1 years and women comprised 84.6% of the patients; in the latter subgroup the corresponding figures were 54.8 and 68.5%. Table 3 represents the regional prevalence rates of hypothyroidism among those patients with low daily levothyroxine consumption.

The number of levothyroxine prescriptions redeemed by a patient per year was an average of 3.4 (mean 3.6 + 1.3). The prescriptions collected annually (that is, compliance with levothyroxine treatment) did not differ substantially between daily consumption subgroups: the mean number of prescriptions purchased per year was 3.5 in patients on 51–150 µg daily levothyroxine doses, 3.7 in those on low doses and 3.6 in those on high doses.

Figure 1 here

Table 3 here

## Discussion

The definite main indication for levothyroxine use is hypothyroidism, which justified evaluating the prevalence of hypothyroidism based on regular levothyroxine purchases. In this nationwide prescription study, 5.9% of females and 1.2% of males

living outside institutions in Finland received levothyroxine medication in 2007. There was no clinically significant regional variation in levothyroxine use between university hospital districts. Our figures correspond well with previous studies that use laborious designs [5,11]. Thus, persistent levothyroxine purchases seem to serve as a readily available and apparently successful estimate of the prevalence of hypothyroidism.

The pattern of thyroid disorders depends partly on genetic factors, but mostly on the level of dietary iodine intake [12]. Finland is generally considered to be a country where people have a sufficient intake of iodine [13], as is Scotland, where subjects with hypothyroidism were identified by electronic linkages between seven databases [11]. Parallel with our figures, the prevalence rates of primary hypothyroidism in that British study were 5.1% in females and 0.9% in males in 2001. In central Norway, where people also have sufficient iodine intake, a large regional health survey between 1995 and 1997 included both questionnaires that asked all participants (20 years and older) eight thyroid-related questions and thyroid blood tests from specific age groups, with the results showing the prevalence rates of formerly-diagnosed hypothyroidism to be 4.8% in women and 0.9% in men [5]. The prevalence of hypothyroidism increased with age among both men and women. Also in line with our study, smaller studies among elderly Nordic subjects confirm the increasing prevalence of hypothyroidism with age, especially in women [12, 14, 15].

The U.S. diet is also acknowledged as being sufficient in iodine. The Framingham Study showed that 13.6% of American women older than 60 years of age had TSH

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3 levels greater than 5 mIU/L [16]. Of the women older than 74 years of age screened at  
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5 a Colorado health fair, 21% had TSH levels greater than 10 mIU/L [4].  
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10 Because of the limits of the survey based on the prescription database, our results may  
11  
12 a bit under- or overestimate the true prevalence of hypothyroidism. We could not  
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14 detect the overall amount of undiagnosed or untreated thyroid deficiency within the  
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16 general population. Lack of data on drug use in nursing homes may also cause us to  
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18 underestimate the extent of the problem, especially among the elderly. On the other  
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20 hand, because of the lack of information about indication for the prescriptions, we  
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22 were not able to exclude subjects who suffered from hypothyroidism secondary to  
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24 treatment for other thyroid disorders. Better interpretation of results requires active  
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26 linkage between registries, for example registry of all hospital admissions [17,18].  
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34 However, other indications than primary hypothyroidism for regular levothyroxine  
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36 use are rare. For example, the incidence of thyroid cancer was 91 in men and 282 in  
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38 women in the year 2007 in Finland and the prevalence of patients with treated thyroid  
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40 cancer as of 1 January 2008 was 1,263 in men and 5,440 in women [18]. Excluding  
41  
42 them afterwards from our calculations of the prevalence of hypothyroidism does not  
43  
44 change our figures. Our nationwide study also included children with rare (1:4000  
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46 live births) congenital hypothyroidism [19]. National cord blood screening for  
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48 congenital hypothyroidism has been done throughout all of Finland since 1980 [20].  
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55 Low levothyroxine dosage can be a sign of the treatment of subclinical  
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57 hypothyroidism [2, 21]. Low daily dosages of levothyroxine did not differ markedly  
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59 between university hospital districts. The optimum dose of levothyroxine when  
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treating overt hypothyroidism is related to bodyweight, about 1.8 µg per kg per day in adults with a benign thyroid disease [22], and age, with a dose requirement that is higher in infants and young children and is lower in older adults. The curve for the mean daily levothyroxine dosage by age in our population logically has the shape of an inverted U. A regular daily dosage of 50 µg or lower in a working-age patient may also be an indicator of inadequate treatment. About 20 % of patients are receiving an inadequate levothyroxine dose for overt hypothyroidism in previous studies [4, 23].

Compliance with levothyroxine treatment is expected to be high because levothyroxine does not have any side effects if the dosage is correct. We used data on medication retrieved from the pharmacy rather than medications prescribed by physicians, thus avoiding primary noncompliance [24].

In Western countries, an increasingly older female population increases also the prevalence of hypothyroidism and its impact on the resources used in primary care, where hypothyroidism is mainly managed. The size and nature (including only patients who are actually being treated) of the comprehensive nationwide prescription database with the elimination of recall and selection bias provides a unique potential for pharmacoepidemiological studies among large populations.

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Table captions:

Table 1 Number of cases and prevalence (per 100 persons in the year 2007) of levothyroxine-treated hypothyroidism by gender and age groups.

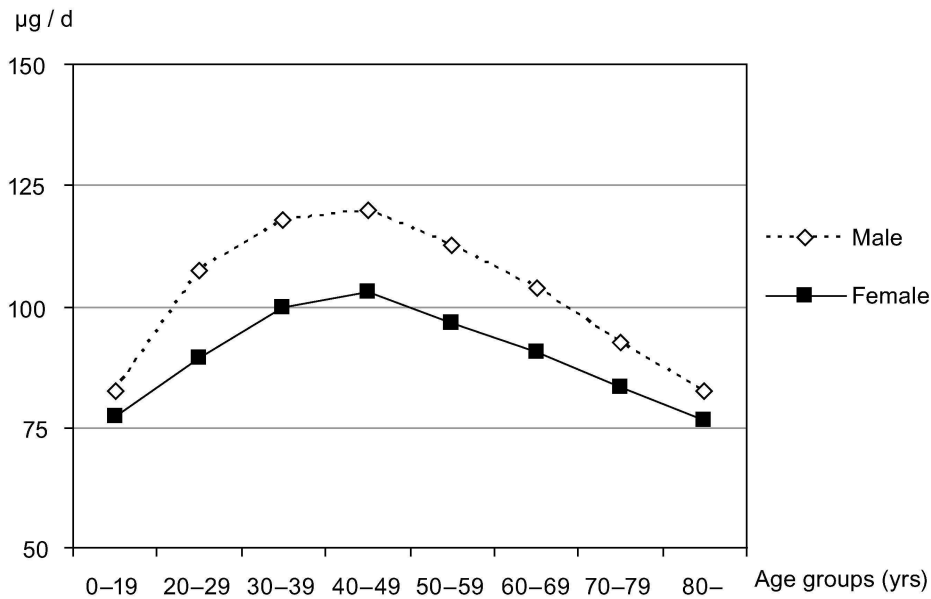
Table 2 Number of cases and one-year (in 2007) prevalence rates (%) of levothyroxine-treated hypothyroidism by university hospital district in Finland.

Table 3 Number of cases and one-year (in 2007) prevalence rates (%) of low levothyroxine daily dosage (<51 µg) users by university hospital district in Finland.

Figure captions:

**Fig. 1** Mean daily dosages (µg /d) of levothyroxine treatment during 2007 by gender and age groups.





Mean daily dosages (µg /d) of levothyroxine treatment during 2007 by gender and age groups.  
121x80mm (600 x 600 DPI)

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**Abstract**

*Purpose* The aim of this study was to estimate the one-year prevalence of levothyroxine-treated hypothyroidism in Finland.

*Methods* From the nationwide Finnish Drug Prescription Database we retrieved all individuals who had regularly purchased the levothyroxine medication during the year 2007. The prevalence rates and 95% CIs were calculated per 100 persons assuming a Poisson distribution.

*Results* Altogether, 189,027 persons (female 84%) used levothyroxine tablets and, hence, the one-year prevalence of hypothyroidism was 3.6%. The disease was notably more common in females (5.9%) than in males (1.2%); the gender prevalence rate ratio (PRR) was 4.5. Prevalence increased with age. Regionally, between five university hospitals districts the prevalence rates were fairly stable, the lowest rate was 3.1% and the highest 4.4%, regional PRR was 1.3.

*Conclusions* To the best of our knowledge, this nationwide prescription study deals with the largest population of reported levothyroxine users to date. This comprehensive data justifies estimating the gender- and age-specific prevalence of hypothyroidism in Finland.

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Table 2 here

The median daily consumption of levothyroxine was 92.3 µg (mean 92.6 ± 40.0 µg per day; 103.1 in males and 90.5 in females). The mean daily dosages were associated with the patients' age (Figure 1). There were 26,219 (13.9%) patients with a low daily dose of levothyroxine (less than 51 µg) and 15,971 (8.4%) patients with a high daily dose (more than 150 µg). In the former subgroup the mean age was 64.1 years and women comprised 84.6% of the patients; in the latter subgroup the corresponding figures were 54.8 and 68.5%. Table 3 represents the regional prevalence rates of hypothyroidism among those patients with low daily levothyroxine consumption.

The number of levothyroxine prescriptions redeemed by a patient per year was an average of 3.4 (mean 3.6 ± 1.3). The prescriptions collected annually (that is, compliance with levothyroxine treatment) did not differ substantially between daily consumption subgroups: the mean number of prescriptions purchased per year was 3.5 in patients on 51–150 µg daily levotyroxine doses, 3.7 in those on low doses and 3.6 in those on high doses.

Figure 1 here

Table 3 here

**Discussion**

The definite main indication for levothyroxine use is hypothyroidism, which justified evaluating the prevalence of hypothyroidism based on regular levothyroxine purchases. In this nationwide prescription study, 5.9% of females and 1.2% of males

living outside institutions in Finland received levothyroxine medication in 2007. There was no clinically significant regional variation in levothyroxine use between university hospital districts. Our figures correspond well with previous studies that use laborious designs [5,11]. Thus, persistent levothyroxine purchases seem to serve as a readily available and apparently successful estimate of the prevalence of hypothyroidism.

The pattern of thyroid disorders depends partly on genetic factors, but mostly on the level of dietary iodine intake [12]. Finland is generally considered to be a country where people have a sufficient intake of iodine [13], as is Scotland, where subjects with hypothyroidism were identified by electronic linkages between seven databases [11]. Parallel with our figures, the prevalence rates of primary hypothyroidism in that British study were 5.1% in females and 0.9% in males in 2001. In central Norway, where people also have sufficient iodine intake, a large regional health survey between 1995 and 1997 included both questionnaires that asked all participants (20 years and older) eight thyroid-related questions and thyroid blood tests from specific age groups, with the results showing the prevalence rates of formerly-diagnosed hypothyroidism to be 4.8% in women and 0.9% in men [5]. The prevalence of hypothyroidism increased with age among both men and women. Also in line with our study, smaller studies among elderly Nordic subjects confirm the increasing prevalence of hypothyroidism with age, especially in women [12, 14, 15].

The U.S. diet is also acknowledged as being sufficient in iodine. The Framingham Study showed that 13.6% of American women older than 60 years of age had TSH

levels greater than 5 mIU/L [16]. Of the women older than 74 years of age screened at a Colorado health fair, 21% had TSH levels greater than 10 mIU/L [4].

Because of the limits of the survey based on the prescription database, our results may a bit under- or overestimate the true prevalence of hypothyroidism. We could not detect the overall amount of undiagnosed or untreated thyroid deficiency within the general population. Lack of data on drug use in nursing homes may also cause us to underestimate the extent of the problem, especially among the elderly. On the other hand, because of the lack of information about indication for the prescriptions, we were not able to exclude subjects who suffered from hypothyroidism secondary to treatment for other thyroid disorders. Better interpretation of results requires active linkage between registries, for example registry of all hospital admissions [17,18].

However, other indications than primary hypothyroidism for regular levothyroxine use are rare. For example, the incidence of thyroid cancer was 91 in men and 282 in women in the year 2007 in Finland and the prevalence of patients with treated thyroid cancer as of 1 January 2008 was 1,263 in men and 5,440 in women [18]. Excluding them afterwards from our calculations of the prevalence of hypothyroidism does not change our figures. Our nationwide study also included children with rare (1:4000 live births) congenital hypothyroidism [19]. National cord blood screening for congenital hypothyroidism has been done throughout all of Finland since 1980 [20].

Low levothyroxine dosage can be a sign of the treatment of subclinical hypothyroidism [2, 21]. Low daily dosages of levothyroxine did not differ markedly between university hospital districts. The optimum dose of levothyroxine when

treating overt hypothyroidism is related to bodyweight, about 1.8 µg per kg per day in adults with a benign thyroid disease [22], and age, with a dose requirement that is higher in infants and young children and is lower in older adults. The curve for the mean daily levothyroxine dosage by age in our population logically has the shape of an inverted U. A regular daily dosage of 50 µg or lower in a working-age patient may also be an indicator of inadequate treatment. About 20 % of patients are receiving an inadequate levothyroxine dose for overt hypothyroidism in previous studies [4, 23].

Compliance with levothyroxine treatment is expected to be high because levothyroxine does not have any side effects if the dosage is correct. We used data on medication retrieved from the pharmacy rather than medications prescribed by physicians, thus avoiding primary noncompliance [24].

In Western countries, an increasingly older female population increases also the prevalence of hypothyroidism and its impact on the resources used in primary care, where hypothyroidism is mainly managed. The size and nature (including only patients who are actually being treated) of the comprehensive nationwide prescription database with the elimination of recall and selection bias provides a unique potential for pharmacoepidemiological studies among large populations.

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Table captions:

- Table 1 Number of cases and prevalence (per 100 persons in the year 2007) of levothyroxine-treated hypothyroidism by gender and age groups.
- Table 2 Number of cases and one-year (in 2007) prevalence rates (%) of levothyroxine-treated hypothyroidism by university hospital district in Finland.
- Table 3 Number of cases and one-year (in 2007) prevalence rates (%) of low levothyroxine daily dosage (<51 µg) users by university hospital district in Finland.

Table 1 Number of cases and prevalence (per 100 persons in the year 2007) of levothyroxine-treated hypothyroidism by gender and age groups.

	Female	Prevalence Rate	Male	Prevalence Rate	Gender
	N	(95% CI)	N	(95% CI)	Prevalence Rate Ratio
Age groups:					
– 19	1,792	0.29 (0.29–0.31)	729	0.12 (0.11–0.13)	2.6
20–29	4,789	1.48 (1.44–1.53)	880	0.26 (0.24–0.28)	5.7
30–39	9,979	3.15 (3.09–3.22)	1,687	0.51 (0.49–0.53)	6.2
40–49	19,058	5.16 (5.09–5.24)	3,595	0.95 (0.92–0.98)	5.4
50–59	34,173	8.63 (8.54–8.73)	6,148	1.56 (1.52–1.60)	5.5
60–69	37,741	12.11 (11.98–12.23)	7,292	2.52 (2.46–2.58)	4.8
70–79	31,151	13.99 (13.84–14.15)	6,499	3.92 (3.83–4.02)	3.6
80–	20,117	13.64 (13.45–13.83)	3,397	5.16 (4.99–5.33)	2.6
All	158,800	5.91 (5.88–5.94)	30,227	1.17 (1.15–1.18)	4.5*

\* adjusted for age

Table 2 Number of cases and one-year (in 2007) prevalence rates (%) of levothyroxine-treated hypothyroidism by university hospital district in Finland.

	Number * of patients	Population at risk	Prevalence rate %	95% CI
<b>University hospital area:</b>				
Turku	31,064	713,071	4.36	(4.31–4.41)
Oulu	28,535	726,883	3.93	(3.88–3.97)
Kuopio	30,763	846,716	3.63	(3.59–3.67)
Tampere	43,011	1,208,581	3.56	(3.53–3.59)
Helsinki	55,549	1,780,267	3.12	(3.09–3.15)
<b>The entire country</b>	<b>189,027</b>	<b>5,275,518</b>	<b>3.58</b>	<b>(3.57–3.60)</b>

\* residence unknown of 105 cases

Table 3 Number of cases and one-year (in 2007) prevalence rates (%) of low levothyroxine daily dosage (<51 µg) users by university hospital district in Finland.

	Number * of patients	Population at risk	Prevalence rate %	95% CI
<b>University hospital area:</b>				
Turku	4,444	713,071	0.62	(0.61–0.64)
Oulu	4,319	726,883	0.59	(0.58–0.61)
Kuopio	3,444	846,716	0.41	(0.39–0.42)
Tampere	5,481	1,208,581	0.45	(0.44–0.47)
Helsinki	8,522	1,780,267	0.48	(0.47–0.49)
<b>The entire country</b>	<b>26,219</b>	<b>5,275,518</b>	<b>0.50</b>	<b>(0.49–0.50)</b>

\* residence unknown of 9 cases

Figure caption:

**Fig. 1** Mean daily dosages (µg /d) of levothyroxine treatment during 2007 by gender and age groups.



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