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Influence of educational level on test and treatment for incident hypothyroidism

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DATA AVAILABLILITY

The data that support the findings of this study are available from Statistics Denmark. Restrictions apply to the availability of these data, which were used under license for this study. Data are available for university-based Danish scientific organisations authorized to work with data within Statistics Denmark and such organisation can provide access to individual scientists inside and outside of Denmark with the permission of Statistics Denmark and the Danish Data Protection Agency.

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SUMMARY

Objective: The prevalence of hypothyroidism is not expected to differ by socioeconomic factors. However, the decision to test and initiate treatment may differ. We aimed to examine whether educational level influences the probability of thyroid stimulation hormone (TSH)-measurement and initiation of levothyroxine treatment.

Design: Citizens in the greater Copenhagen Area during 2001-2015 were included. Individual-level data on educational level, diagnoses, GP-contact, TSH-measurement, and medication were derived from administrative and health care registers. The relative risks (RR) between educational levels of annual TSH-measurement and treatment initiation following a TSH-measurement were analyzed in Poisson regression models with generalized estimation equations.

Results: A TSH-measurement was performed in 19% of 9,390,052 person years. The probability of TSH-measurement was higher with short (RR 1.16 (95%CI 1.15-1.16)) and medium (RR 1.11 (95%CI 1.06-1.12)) compared with long education.

Treatment was initiated after 0.8% of 2,049,888 TSH-measurements. For TSH <5 mIU/L RR for treatment initiation ranged between 0.47 (95%CI 0.39-0.57) and 0.78 (95%CI 0.67-0.91) for short and medium compared with long education. For TSH 5-10 mIU/L there was no statistically significant difference. For TSH >10 mIU/L RR was 1.07 (95%CI 1.02-1.12) for short and 1.08 (95%CI 1.03-1.13) for medium compared with long education.

Conclusion: The probability of TSH-measurement was higher with shorter education and the probability of treatment initiation with TSH >10 mIU/L was marginally higher with short-medium education compared with long education. However, the probability of treatment initiation with TSH <5 mIU/L, i.e. treatment incongruous with guidelines, was substantially higher in persons with long education.

Keywords: socioeconomic factors, hypothyroidism, thyroid function tests, levothyroxine

INTRODUCTION

Social inequality in health care explains a large proportion of the inequality in health and life expectancy.[1] Social inequality in treatment is observed for several diseases in Denmark and persists despite universal free health care.[2] Most tests and treatments for hypothyroidism are conducted at the general practitioner (GP).[3] Hypothyroidism is common with a prevalence of 1-2% in iodine-replete populations,[4] and treatment with levothyroxine has doubled during the two past decades.[5] Nevertheless, few studies have examined social inequality in test and treatment for hypothyroidism. Elucidation of the influence of socioeconomic status on test and treatment is essential in the process towards equity in health.

Social inequality in disease is divided into two categories: inequality in the risk of disease and inequality in treatment. There is likely to be little socioeconomic difference in the risk of hypothyroidism because both iodine intake[6,7] and subclinical hypothyroidism[8] have been found to be independent of socioeconomic factors in areas with efficient iodine fortification and iodine repletion, respectively. However, the decision to test and treat for hypothyroidism partly rely on factors that may increase the risk of social inequality. Symptoms of hypothyroidism are not objectively measured, occur frequently in euthyroid persons, and have little diagnostic power for hypothyroidism.[9] The European Thyroid Association (ETA) guidelines recommend treatment with levothyroxine for overt hypothyroidism (high s-TSH and low s-T4) in patients <70 years and for subclinical hypothyroidism (high s-TSH and normal s-T4) with symptoms in patients <65 years[10] but the threshold for treatment initiation is debated.[11,12]

In the greater Copenhagen Area incident overt hypothyroidism increased by 30% after iodine fortification in 2000.[13] Concurrently, incident treatment for hypothyroidism increased by 75% from 2000 until 2010, where it plateaued.[5] This gap is primarily due to treatment initiation at lower TSH-thresholds and secondarily due to more tests of TSH.[14] However, it is not known whether the increase in tests and decrease in threshold for treatment are equal across socioeconomic groups or more prominent in some groups.

Educational level will be utilized as the measure of socioeconomic status in this study because it is an underlying determinant for other socioeconomic measures.[15] Furthermore, education may make persons "*more able to communicate with and access appropriate health services*".[16]

The primary aim of this study was to examine whether educational level is associated with TSH-measurement and initiation of levothyroxine treatment. Secondarily, we aimed to analyze changes in these potential relations during 2001-2015.

MATERIALS AND METHODS

Study populations

We included all citizens aged ≥25 in the Copenhagen Municipality and the former Copenhagen County on the 1st of January for each year 2001-2015.

We examined annually whether a TSH-measurement was conducted after a GP-contact as part of a medical examination for incident disease. Observations were excluded if there was a) current or previous diagnosis of hyperthyroidism (ICD-10: DE05.0-9), thyroid cancer (ICD-10: DC73.9), or pituitary disease (ICD-10: DE23.0-9); b) a redeemed prescription of thyroid-interfering drugs within six previous months (amiodarone (ATC: C01BD01), lithium (ATC: N05AN01), propylthiouracil (ATC: H03BA02), thiamazole (ATC: H03BB01), carbimazole (ATC: H03BB01), monoclonal antibodies (ATC: L01XC), and protein kinase inhibitors (ATC: L01XE)), c) a redeemed prescription of levothyroxine (ATC: H03AA) within three previous years, or; d) a birth or abortion (ICD-10: DO03.0-9) within 12 months before or after.[14] Observations with unknown educational level were excluded.

Likewise, we examined whether incident treatment was initiated after a TSH-measurement requested by a GP. TSH-measurements were excluded if they met one of the criteria a)-d) described above. If two TSH-measurements were performed within four months only the last was included as the measurements were regarded part of the same examination.[14] Finally, TSH-measurements with missing TSH-values or unknown educational level were excluded.

The flow of in- and excluded observations is illustrated in **Figure 1**.

Data sources

All GPs in the Copenhagen Municipality and former Copenhagen County were serviced by one laboratory during 2000-2015. The Copenhagen Primary Care Laboratory (CopLab) Database contains results from all tests and analyses performed,[17] and we utilized data on TSH-measurements. Furthermore, we utilized individual-level data from nationwide administrative population and healthcare registers. Registries at Statistics Denmark contain information on educational level,[18] municipality of residence, age, and sex[19] and is updated annually. The Danish National Patient Register (NPR) contains diagnoses for all in- and out-patient hospital contacts since 1977.[20] The Danish National Prescription Registry (DNPR) contains records of all redeemed prescriptions since 1995,[21] and The National Health Service Register contains records of all contacts to GPs since 1990.[22] Individual-level linkage between CopLab data and nationwide registers is possible via the unique civil registration number assigned to all Danish citizens.[19]

Ethical and data handling approval was obtained at the Faculty of Health Science, University of Copenhagen (case no. 514-0244/18-3000).

Outcome variables

TSH-measurement was defined as at least one TSH-measurement in a year conducted within 30 days of a GP-contact. TSH-measurement was recorded for the year of the GP-contact closest to the measurement. Treatment initiation was defined as a redeemed prescription of levothyroxine (ATC: H03AA) within six months following a TSH-measurement. Treatment initiation was recorded for the TSH-measurement closest to a first redeemed prescription.

Education, age, sex, municipality, and comorbidities

Highest attained educational level was divided into three categories according to the International Standard Classification of Education (ICSED) levels: short education (primary or upper secondary education), medium education (>4 years; vocational education), and long education (≥4 years: bachelor's or master's degree or short-cycle higher education). Information on age, sex and municipality of residence was obtained from the Civil Registration System. The Charlson comorbidity index (CCI) as updated in 2011[23,24] was calculated for each observation as a cumulative weighted score (maximum 24) from the number and severity of comorbid conditions. Primary and secondary diagnoses during the two previous years were derived from the NPR, and the CCI was calculated using a SAS macro (developed by Ken Turner and Charles Burchill).[25] The CCI was classified into 0(none) and ≥1. For each observation, all variables were defined annually.

TSH analyses

TSH measurements were performed in one laboratory and was determined in serum by the commercially available ADVIA Centaur/CentaurXP method (Bayer/ Siemens, Tarrytown, NY) with a coefficient of variation of 4,9-6,3%. The method has been described in more detail previously.[14] The normal range of TSH-measurements reported to GPs was 0.2–5.0 mIU/l. Observations outside the reported lower (<0.02 mIU/L) and upper (>135 or >150 mIU/L) detection limit were included with their value set to the value of the limit.[14]

Statistical analyses

Population characteristics are presented for the total population and stratified by educational level. Poisson regression with robust standard errors was applied to assess the relative risk (RR) and 95% confidence intervals (95% CI) for the associations between educational level and TSH-measurement and treatment initiation. Because each person may be found in the datasets more than once (once every year and with more than one TSH-measurement), one person constitutes a cluster, and thus Generalized Estimating Equations were applied to correct for clusters of correlated observations. The independent correlation structure provided the best fit evaluated by the QIC-value. Dose-response relationships were assessed by testing the linear effect of the ordinal variable. Effect measure modifications were assessed by testing the interaction terms and the joint effects derived from the models are presented.

Analyses of the association between educational level and TSH-measurement within a person year was adjusted for sex, age, CCI, and calendar year. The effect of calendar year (split into five 3-year levels) was tested by adding the interaction with educational level to the model one pair at a time. In sensitivity analyses the model was further adjusted for the mediator 'number of GP-contacts within a year'.

Analyses of the association between educational level and treatment initiation were adjusted for sex, age, CCI, TSH-level, calendar year, and the interaction between educational level and TSH-level. The effect of calendar year (split into five 3-year levels) was explored by adding the 3-way interaction between educational level, TSH-level, and calendar year.

Analyses were performed in SAS, version 9.4 (SAS Institute Inc, Cary, NC, USA) and statistical significance defined as $p < 0.05$.

RESULTS

Descriptive statistics of characteristics of the populations are presented according to educational level in **Table 1**. Persons with shorter education had higher age and more frequently had a CCI ≥1. The number of GP-contacts within one year was higher with shorter education. The level of TSH did not differ markedly between educational levels (**Table 1**). The number of person years increased during the study period in the group with longer education but not in the other groups. The number of TSH-measurements increased during the study period for all educational levels but relatively more in the group with longer education (**Table 1**). This is partly explained by more persons with long education in the greater Copenhagen Area during the study period (**Supplementary Table S1**).

TSH-measurement

A TSH-measurement was performed in 19% (1,805,300/ 9,390,052) of the person years. The probability of TSH-measurement was higher in persons with short and medium education, RR 1.16 (95%CI 1.15-1.16) and RR 1.11 (95%CI 1.06-1.12), respectively, compared with long education (**Table 2**) with a clear dose-response relationship (p for trend <0.001).

There was a statistically significant effect of the interaction between educational level and calendar year. During the study period, the RR for TSH-measurement increased for both short and medium education compared with long education in the same year and fell back to approximately the same level (**Figure 2**).

When adjusting for the number of GP-contacts per year the estimates decreased marginally.

Supplementary analyses found a higher probability of TSH-measurement with higher age, in women, with lower income, and a marginally higher probability of TSH-measurement in persons living without a partner (**Supplementary Material S2 and Table S3**).

Treatment initiation

Treatment was initiated after 0.8% (16,992/2,049,888) of the TSH-measurements. The probability of treatment initiation was lower following TSH-measurements in persons with short or medium education compared with long education for TSH <0.4, 0.4-2.5, and 2.5-5 mIU/L with RR ranging between 0.47 (95%CI 0.39-0.57) and 0.78 (95%CI 0.67-0.91). There was no difference in the probability of treatment initiation between the educational levels with TSH 5-10 mIU/L and a marginally higher probability of treatment initiations in persons with short or medium education compared with long education for TSH >10 mIU/L with RR 1.07 (95%CI 1.02-1.12) and 1.08 (95%CI 1.03-1.13) for short and medium education, respectively. The probability of treatment initiation was similar for short and medium educational level for all TSH-levels (**Table 3**).

There was a statistically significant effect of the 3-way interaction between educational level, TSH-level, and calendar year: For TSH <0.4 and 2.5-5 mIU/L, the probability of treatment initiation was consistently lower for persons with short or medium education compared with long education during the study period. For TSH 0.4-2.5 mIU/L, the probability of treatment initiation for short and medium education was higher in 2001-2003 and lower from 2007 compared with long education. For TSH 5-10 and >10 mIU/L, the probability of treatment initiation was lower and higher, respectively, for short and medium education before 2006 and largely similar to the probability for long education after 2007 (**Figure 3**).

Supplementary analyses found a higher probability of treatment initiation with lower age, in women, and a marginally higher probability of treatment initiation in persons living with a partner for all levels of TSH. The probability of treatment initiation was higher with higher income for TSH <0.4 and 2.5-5 mIU/L while there was no difference for TSH 0.4-2.5 and >5 mIU/L (**Supplementary Material S2 and Table S4-S7**).

DISCUSSION

The current knowledge of socioeconomic inequality in tests and treatments of hypothyroidism is limited despite frequent and increasing use of both TSH-measurements and levothyroxine treatment. In this first large population-based register study on the topic, we found that the probability of a TSH-measurement within a year was highest in persons with shorter education. However, the probability of treatment initiation was highest following TSH-measurements in persons with longer education for lower levels of TSH and slightly higher for higher levels of TSH.

Contact with the GP is a necessary first step before thyroid function test and treatment. In additional analyses, we found a 1-3% higher probability of having one or more GP-contacts within a year for short and medium education compared with long education (**Supplementary Material S1 and Table S2**). This indicates that social inequality does not markedly influence this step in health care for hypothyroidism.

We identified only one previous study on the association between socioeconomic characteristics and treatment for hypothyroidism. In a population of 14,590 civil servants from six Brazilian cities, the frequency of hypothyroidism defined by elevated TSH and/or prevalent levothyroxine use did not differ by educational level or income. But interestingly, the use of levothyroxine was significantly associated with higher income with an odds ratio of 3.34 (1.48-7.57) for medium income and 3.07 (1.01-9.38) for high income compared with low income after adjustment.[26] However, their data does not reveal if this is due to differences in tests, treatments, or both. Furthermore, the mechanisms underlying the effect of income may differ between the Danish and the Brazilian healthcare systems.

Educational level was chosen as the socioeconomic exposure because it is a determinant for other sociodemographic factors.[15] Measurement of educational level attempts to capture knowledge, cognitive skills, and analytical abilities,[16] which may influence the acquisition of health information and interaction with GPs and thus the decision to test and treat. Income captures material resources available to the individual,[16] which is less relevant in a Danish context with free universal health care and a relatively low cost of levothyroxine treatment (EUR 35.5/user/year in 2015 prices).[27] Yet, similar results were found for income in supplementary analyses.

It is interesting to note that among the lower levels of TSH, short and medium education had a lower probability of treatment initiation compared with long education. Treatment initiation with TSH <5 mIU/L is considered inappropriate in this patient group (excluding patients with previous thyroid cancer and plans of pregnancy) according to guidelines.[10] In a survey among 539 physicians, 46% reported patient's requests for tests and treatment as a barrier to proper management of hypothyroidism only surpassed by patient non-adherence (70%). Patients requested e.g. adjusting thyroid hormone dose based on symptoms when biochemically euthyroid and maintaining TSH below the reference range. Physicians receiving these requests were more likely to execute this practice.[28] It may be speculated that persons with long education are more prone to request treatments discrepant with guidelines or decline indicated treatments.

Treatment initiation with TSH within the reference range may for few cases be due to treatment for goiter or subacute thyroiditis. Moreover, levothyroxine is occasionally used to treat depression, overweight, tiredness or other symptoms of hypothyroidism in euthyroid persons despite recommendations. This practice is hypothesized to be more frequent in persons with long education due to requests and/or an increased awareness in this group of discussions of subclinical hypothyroidism.

Even though the absolute number of persons initiating treatment with suppressed TSH is low, the implications are serious as overtreatment of hypothyroidism is associated with an increased risk of atrial fibrillation, osteoporotic fractures,[29] and all-cause mortality.[30]

Among subjects with high levels of TSH, short and medium education had a higher probability of treatment initiation compared with long education. Part of this difference may be explained by subclinical hypothyroidism for which the ETA recommends treatment in persons ≤70 years and consideration of treatment in person >70 years with clear symptoms of hypothyroidism or high vascular risk.[10] Symptoms and vascular risk factors are more frequent with shorter education[31] and may affect the probability of treatment initiation as we were unable to adjust for this.

Through the study period, the inequality in TSH-measurements rose and fell. The development in the inequality in treatment initiation differed between levels of TSH: For TSH <0.4 mIU/L and 2.5-5 mIU/L the inequality remained relatively constant while for TSH 0.4-2.5 mIU/L the inequality changed direction. Both TSH 5-10 mIU/L and >10 mIU/L approached no inequality after 2006. This may be driven by the implementation of mandatory measurement of thyroid peroxidase (TPO)-antibodies if s-TSH was >5 mIU/L and free thyroxine was within the reference range from December 2006.[14] In contrast with symptoms and vascular risk factors, TPO-antibodies are not assumed to be associated with educational level. Treatment decisions for subclinical hypothyroidism based on TPO-antibodies (despite this not being recommended by the ETA[10]) may thus minimize educational differences.

Strengths and limitations

The main strength of this study is the large sample size and utilization of individual-level register data of good validity[32] along with well-documented laboratory data from GPs, which is rarely available. There is limited risk of confounding by geographic differences in access to health care because the whole population lives in the greater Copenhagen Area. It is a limitation that data were not available for symptoms, fT4, fT3, and anti-TPO to ascertain the specific indication for TSH-measurement and treatment. Somatic symptoms are more frequent with lower educational level[31] and unspecific symptoms such as tiredness may influence the decision to measure TSH and/or initiate treatment. Although, somatic symptoms are closely associated with the presence of comorbidities[31] they may not be sufficiently adjusted for through the CCI. We were unable to include data on smoking. Smoking is more frequent with short education and increases the risk of hypothyroidism[33], thus, the GP's knowledge of smoking status may be a confounder in the association between educational level and TSH-measurement. Smoking will be reflected in the TSH-level[34] and should therefore not further influence the decision to initiate treatment.

In conclusion, the results indicate that the probability of TSH-measurement is consistently higher with shorter education. The probability of treatment initiation with high levels of TSH was marginally higher with short and medium education compared with long education. However, these inequalities approached 0 during the study period and are thus of less concern. The probability of inappropriate treatment initiation with low or normal TSH-levels is substantially higher in persons with long education, and these inequalities are of concern as they persist throughout the study period. This warrants further studies to elucidate the motivation for treatment initiation with low and normal TSH to prevent overtreatment. Further, this is only the second study of inequalities in test and treatment of hypothyroidism, and this should be repeated in populations with different health care systems.

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Table 1: Characteristics of person years with minimum one GP-contact and TSH-measurements during 2001-2015.

	Person years with minimum one GP-contact during 2001-2015										TSH-measurements during 2001-2015									
Characteristics			**Educational level**										**Educational level**							
	Total		**Short**		**Medium**		**Long**		**Unknown**		**Total**		**Short**		**Medium**		**Long**		**Unknown**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Age																				
25-34	2,331,684	24	715,533	24	536,928	18	1,004,141	30	75,082	15	274,986	13	89,342	12	60,050	9	114,255	18	11,339	8
35-44	2,094,423	21	553,943	18	624,238	21	862,962	26	53,280	10	339,190	15	98,921	14	98,959	14	130,195	20	11,115	8
45-54	1,765,066	18	517,813	17	579,963	19	621,700	19	45,590	9	395,324	18	123,484	17	129,561	19	129,162	20	13,117	9
55-64	1,553,066	16	474,810	16	577,561	19	468,253	14	32,442	6	418,030	19	131,839	18	152,073	22	124,404	20	9,714	7
65-74	1,143,934	12	412,564	14	440,556	15	255,531	8	35,283	7	379,695	17	136,879	19	145,181	21	85,663	13	11,972	8
75-84	715,500	7	290,131	10	230,415	8	114,683	3	80,271	16	265,620	12	110,595	15	89,299	13	43,719	7	22,007	15
85+	301,408	3	52,457	2	36,578	1	19,292	1	193,081	37	120,516	6	27,464	4	18,912	3	9,931	2	64,209	45
Sex																				
Men	4,471,158	45	1,354,062	45	1,493,336	49	1,427,265	43	196,495	38	816,408	37	249,436	35	288,790	42	235,171	37	43,011	30

Women	5,433,923	55	1,663,189	55	1,532,903	51	1,919,297	57	318,534	62		1,376,953	63	469,088	65	405,245	58	402,158	63	100,462	70
CCI																					
0	9,299,739	94	2,789,529	92	2,832,267	94	3,227,630	96	450,313	87		2,007,438	92	646,022	90	634,466	91	604,087	95	122,863	86
≥1	605,342	6	227,722	8	193,972	6	118,932	4	64,716	13		185,923	8	72,502	10	59,569	9	33,242	5	20,610	14
Number of GP-contacts per year																					
1-3	2,469,709	25	696,266	23	730,699	24	950,179	28	92,565	18		-	-	-	-	-	-	-	-	-	-
4-6	1,936,720	20	552,647	18	588,760	19	715,688	21	79,625	15		-	-	-	-	-	-	-	-	-	-
7-9	1,409,320	14	412,710	14	434,192	14	497,548	15	64,870	13		-	-	-	-	-	-	-	-	-	-
>10	4,089,332	41	1,355,628	45	1,272,588	42	1,183,147	35	277,969	54		-	-	-	-	-	-	-	-	-	-
TSH, mIU/L																					
<0.4	-	-	-	-	-	-	-	-	-	-		75,971	3	28,199	4	23,340	3	15,250	2	9,182	7
0.4-2.5	-	-	-	-	-	-	-	-	-	-		1,706,513	78	555,618	77	544,498	78	500,110	78	106,287	74
2.5-5.0	-	-	-	-	-	-	-	-	-	-		349,342	16	113,472	16	107,839	16	105,325	17	22,706	16

5.0-10	-	-	-	-	-	-	-	-	-	-	49,826	2	17,257	2	14,806	2	13,557	2	4,206	3
>10	-	-	-	-	-	-	-	-	-	-	11,709	1	3,978	1	3,552	1	3,087	0	1,092	1
Calendar year																				
2001-2003	1,806,429	18	607,611	20	563,249	19	479,565	14	156,004	30	248,997	11	86,675	12	74,966	11	52,144	8	35,212	25
2004-2006	1,823,708	18	597,070	20	569,647	19	541,013	16	115,978	23	344,452	16	120,167	17	109,036	16	81,910	13	33,339	23
2007-2009	2,049,431	21	626,545	21	635,843	21	691,824	21	95,219	18	437,606	20	147,801	21	141,893	20	120,499	19	27,413	19
2010-2012	2,083,410	21	601,943	20	630,371	21	770,372	23	80,724	16	533,361	24	172,597	24	170,749	25	164,921	26	25,094	17
2013-2015	2,142,103	22	584,082	19	627,129	21	863,788	26	67,104	13	628,945	29	191,284	27	197,391	28	217,855	34	22,415	16

N number of observations, GP general practitioner, TSH thyroid stimulating hormone, CCI Charlson comorbidity index

Each person contributes person years every year with a GP-contact, i.e. between 1-15 person years.

Table 2: Relative risk for TSH-measurement

Educational level					
Short		Medium		Long	
% (years with TSH-measurement/years total)	RR (95%CI)	% (years with TSH-measurement/years total)	RR (95%CI)	% (years with TSH-measurement/years total)	RR (95%CI)
21 (632,694/3,017,251)	1.16 (1.15-1.16)	20 (614,387/3,026,239)	1.11 (1.06-1.12)	17 (558,219/3,346,562)	1 (ref.)

RR relative risk, CI confidence interval

RR estimates from the model including educational level, sex, age, CCI, and calendar year

Table 3: Relative risk of treatment initiation

	Educational level					
	Short		Medium		Long	
TSH, mIU/L	% (treatment initiation/TSH-measurements)	RR (95%CI)	% (treatment initiation/TSH-measurements)	RR (95%CI)	% (treatment initiation/TSH-measurements)	RR (95%CI)
<0.4	0.63 (179/28,199)	0.47 (0.39-0.57)	0.65 (152/23,340)	0.48 (0.39-0.59)	1.59 (242/15,250)	1 (ref.)
0.4-2.5	0.06 (309/555,618)	0.78 (0.67-0.91)	0.05 (259/544,498)	0.69 (0.59-0.80)	0.08 (403/500,110)	1 (ref.)
2.5-5	0.29 (333/113,472)	0.57 (0.50-0.66)	0.27 (289/107,839)	0.54 (0.47-0.62)	0,19 (610/105,325)	1 (ref.)
5-10	16.22 (2,799/17,257)	0.96 (0.91-1.00)	17.10 (2,532/14,806)	1.01 (0.96-1.06)	19.49 (2,642/13,557)	1 (ref.)
>10	56.44 (2,245/3,978)	1.07 (1.02-1.12)	57.85 (2,055/3,552)	1.08 (1.03-1.13)	62.94 (1,943/3,087)	1 (ref.)

RR relative risk, CI confidence interval

Joint effect RR estimates from the model including educational level, sex, age, TSH-level, calendar year, and the interaction between TSH-level and educational level

Figure legends

Figure 1: Flow chart of in- and excluded observations for analyses of a) the association between educational level and TSH-measurement, and b) the association between educational level initiation of levothyroxine treatment.

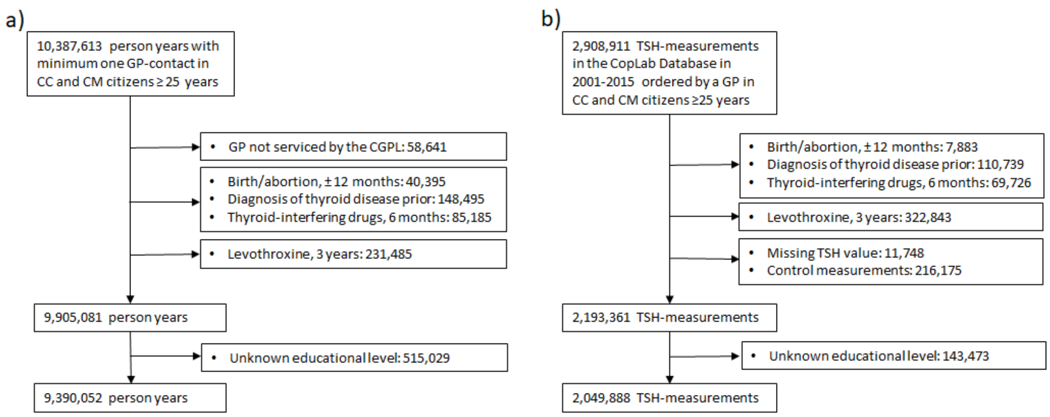
GP general practitioner, CC and CM Copenhagen County and Copenhagen Municipality, CGPL Copenhagen General Practitioners' Laboratory, TSH thyroid stimulating hormone

Figure 2: Relative risk and 95% confidence intervals for TSH-measurement for short and medium education compared with long education within each 3-year period. Joint effect RR estimates from the model including educational level, sex, age, CCI, calendar year, and the interaction between educational level and calendar year.

RR relative risk

Figure 3: Relative risk and 95% confidence intervals for treatment initiation for short and medium education compared with long education within each 3-year period. Joint effect RR estimates from the model including educational level, sex, age, CCI, TSH-level, calendar year, and the 3-way interaction between educational level, TSH-level, and calendar year

RR relative risk, TSH thyroid stimulating hormone



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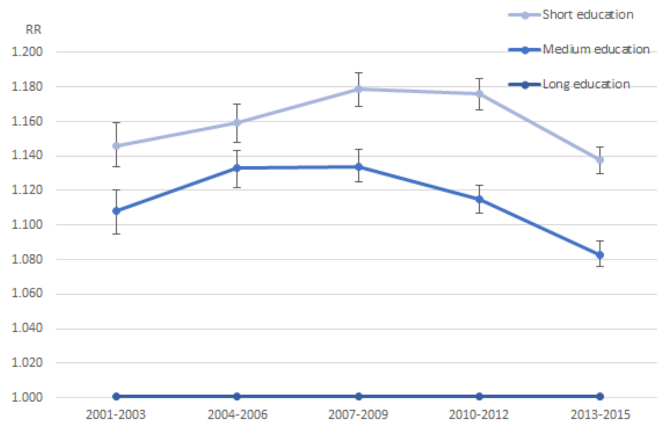

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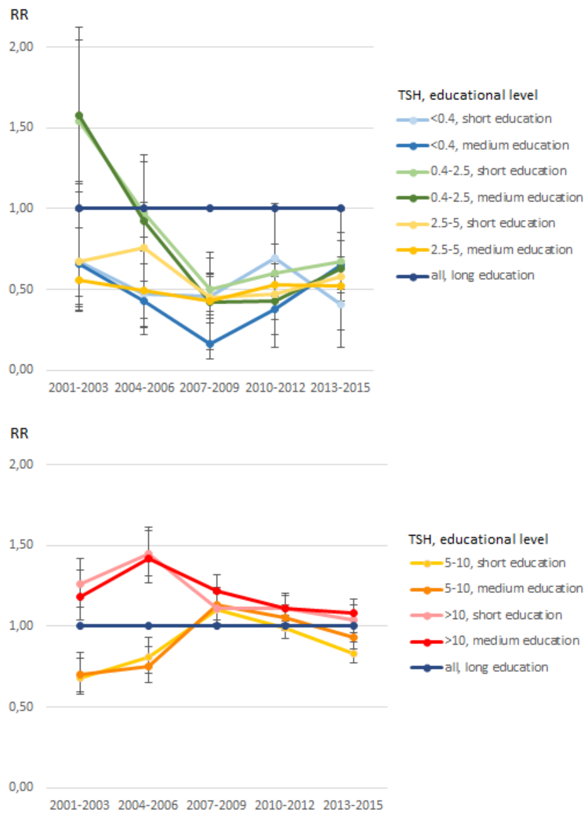

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