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Title: Over-use of thyroid testing in Canadian and UK primary care in frequent attenders: a cross-sectional study

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Abstract

Background

Thyroid stimulating hormone (TSH) is a common test used to detect and monitor clinically significant hypo- and hyperthyroidism. Population based screening of asymptomatic adults for thyroid disorders is not recommended.

Objective

The research objectives were to determine patterns of TSH testing in Canadian and English primary care practices, as well as patient and physician practice characteristics associated with testing TSH for primary care patients with no identifiable indication.

Methods

In this two-year cross-sectional observational study, Canadian and English electronic medical record databases were used to identify patients and physician practices. Cohorts of patients aged 18 years or older, without identifiable indications for TSH testing, were generated from these databases. Analyses were performed using a random-effects logistic regression to determine patient and physician practice characteristics associated with increased testing. We determined the proportion of TSH tests done concurrently with at least one common screening blood test (lipid profile or hemoglobin A1c). Standardized proportions of TSH test per family practice were used to examine the heterogeneity in the populations.

Results

At least one TSH test was done in 35.97 % (N=489,663) of Canadian patients and 29.36% (N=1,030,489) of English patients. Almost all TSH tests in Canada and England (95.69% and 99.23% respectively) were within the normal range (0.40-5.00 mU/L). A greater number of patient-physician encounters was the strongest predictor of TSH testing. 51.40% of TSH tests in Canada and 76.55% in England were done on the same day as at least one other screening blood test. There was no association between practice size and proportion of asymptomatic patients tested.

Conclusions

This comparative binational study found TSH patterns suggestive of over-testing and potentially thyroid disorder screening in both countries. There may be significant opportunities to improve appropriateness of TSH ordering in Canada and England and therefore improve allocation of limited system resources.

What's already known about this topic?

- Population-based screening of asymptomatic adults for thyroid disorders is not recommended and yet it accounted for the second-highest laboratory costs after microbiology cultures in Ontario, Canada.

- Previous study using localized primary care data found high rates of TSH testing among asymptomatic adults for thyroid disorders and demonstrated modest reduction in TSH testing using site-level clinical guidelines on TSH testing.

What does this article add?

- To our knowledge, no research study has been conducted to examine the extent of TSH testing at national scale. This study estimated the TSH testing using bi-national primary care in Canada and UK.

- This goal of this study is to raise awareness on the over-use of low-valued clinical tests at the national scale (e.g. TSH testing among asymptomatic patient population). Future research efforts may focus on the implementation of national clinical guidelines to reduce unnecessary screening tests in primary care.

Keywords: primary care; thyroid testing; cross-sectional study

Introduction

Physicians are trained to investigate and diagnose patients living with thyroid disorders. Thyroid disorders are a set of clinical conditions which occur due to abnormal circulating levels of thyroid gland-generated hormones such as thyroxine [T4] or triiodothyronine [T3]. Patients with symptomatic, untreated hypo or hyperthyroidism can acquire deleterious sequelae such as cardiac conditions and cognitive dysfunction.(3) Identifying those patients and treating them represents ideal clinical care. Recent media reports have highlighted cases of missed diagnoses of thyroid disorders, which may increase pressure on physicians to find cases of thyroid disorder in their patient population.(1, 2) However, many patients have subclinical, asymptomatic thyroid dysfunction and many will revert to normal thyroid function over time without treatment.(4, 5) Evidence is lacking to suggest a clear link between subclinical thyroid dysfunction and any significant negative health outcomes including mortality.(5, 6)

Notwithstanding the potential challenges of detecting thyroid disease, particularly hypothyroidism, there are clear guidelines as to when thyroid testing should be conducted in primary care. Population based screening of asymptomatic adults for thyroid disorders is not recommended.(5, 6) The annual incidence of thyroid disorders is less than 1%;(7) screening may lead to unnecessary treatment and increased use of resources, with no resulting improvement in patient outcomes.(4, 6) The US Preventive Services Task Force found insufficient evidence for or against screening(4). Guidelines endorsed by Choosing Wisely Canada, the College of Family Physicians of Canada, the Canadian Task for on Preventive Health Care and the UK's National Institute for Clinical Excellence all advise against ordering thyroid function tests in asymptomatic patients.(6, 8, 9)

The recommended test for the detection of hypothyroidism or hyperthyroidism is a Thyroid Stimulating Hormone (TSH)(10). Circulating thyroid hormones feed back to the pituitary gland to regulate production of TSH, which drives production of thyroid hormones by the thyroid gland. TSH testing is considered more accurate at confirming hypothyroidism or hyperthyroidism when compared to direct tests for T3 or T4. TSH tests are ordered frequently: a 1996 report from Ontario, Canada found that it accounted for the second highest laboratory costs after microbiology cultures.(11) Due to concerns about possible overuse, the province of Ontario in 2012 removed a checkbox for simplified ordering of the TSH test on their standardized lab requisition form.(12) There is documentation of large practice variations in TSH ordering in the UK(13) and two recent studies in family practices in or near Toronto, Ontario found significant overuse of TSH test.(14, 15)

To our knowledge, there are no studies using large, nationally representative samples that consider patterns of TSH ordering in patients without identifiable symptoms in primary care. Comparing Canada and England, two high-income countries, is a useful benchmarking exercise for this specific example of health system utilization because their primary care systems share many common features. For instance, in both Canada and England, primary care is publicly financed but provided within privately operated physician practices, staffed with general practitioners (or analogously family

physicians) with a context where well-respected professional organizations have provided similar recommendations against screening for thyroid disorders in asymptomatic patients.(16, 17)

Our aim was to describe TSH testing patterns in adult patients with no identifiable indication in Canadian and English primary care settings and to evaluate physician practice and patient characteristics associated with TSH testing.

Methods:

Study Design

This was a repeated cross-sectional observational study design using routinely collected electronic medical record (EMR) data in primary care. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist was applied to report the results of this study.(18)

Settings and Data sources

Routinely collected clinical EMR data from primary care clinics in Canada and England were used. Canadian data were obtained from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN), with data extracted up to July 1st 2017. (19) CPCSSN is Canada's largest EMR-based chronic disease surveillance system;(19) it includes data from eleven primary care practice based research networks in eight provinces. Consenting family physicians and other primary care providers participating in CPCSSN contribute de-identified EMR data to a regional CPCSSN repository; patients can opt-out if they choose to do so. Data from all participating networks are aggregated in a single central database.(19, 20) The demographic characteristics of the CPCSSN patient population can be age and gender adjusted to create a sample that is representative of the Canadian general population.(21)

The analyses were carried out in parallel using the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) database for England. Data were extracted as of December 31st, 2017. The RCGP RSC database is one of the oldest European data repository and contains EMRs for 3.2 million patients with 2.3 billion consultations.(22) The RCGP RSC database contains high quality data for incidence and prevalence based metrics of many chronic diseases, including diabetes and cardiovascular outcomes.(22) Previous work has also shown that age, gender, ethnicity and deprivation index of the RCGP RSC database are representative of national England population from 2011 census data.(22)

Study population

Patients aged 18 or older as of January 1st, 2016 with at least one clinical visit in the two-year observational period were included. Based on criteria established in previous studies, (15) patients were excluded if there were clearly identifiable

indications for TSH testing in their EMR record at any time starting from January 1, 2010 to the end of the study observation period June 30, 2017. These indications included a historical diagnosis of thyroid disease (hyperthyroid, hypothyroid, thyroid cancer) in the EMR or at least one prescription for thyroid replacement therapy. Patients were also excluded if they were on medications (related to hypo- and hyperthyroidism), had a diagnosis that may be associated with thyroid dysfunction, or were clinically indicated such as for monitoring while on amiodarone or lithium prescriptions or for current or recent pregnancy or infertility.(23) While primary care EMR data cannot fully differentiate between tests done for screening versus tests based on clinical suspicion of thyroid dysfunction during clinical encounters, an attempt was made to identify and exclude tests done for clinical suspicion by searching for diagnoses that may prompt testing: anxiety, tachycardia, fatigue, insomnia, abnormal weight gain, hair loss or galactorrhea.(23)

Three CPCSSN networks did not collect TSH tests during the study period and were excluded from the analysis. Providers who did not have any patients with TSH data during the two years of interest were also excluded.

The outcome was at least one TSH test during the two years prior to the date of extraction (i.e. end of study follow-up): July 1st, 2015 to June 30th, 2017 for Canada and January 1st, 2016 to December 31st, 2017 for England. A normal TSH was defined as a value ≥0.4 and ≤ 5 mU/L; an abnormal, hyperthyroid TSH was defined as a value < 0.4 mU/L while an abnormal, hypothyroid TSH was defined as a value > 5 mU/L.

We evaluated variables that may influence TSH testing:(15) age, sex, number of face-to-face consultations, presence of co-morbidities such as depression, dementia or rheumatoid arthritis,(23) overall number of co-morbidities and most recent body mass index (BMI). We also considered the possibility of a screening approach being undertaken by measuring the prevalence of bundling of TSH testing with other laboratory tests used for screening or management of chronic diseases common in primary care settings. We considered bundling for screening if a TSH was done concurrently with a lipid profile (total cholesterol, serum triglyceride)(24) or hemoglobin A1c.(25)

Statistical analysis:

Random-effects logistic regression was used to determine patient characteristics associated with TSH test ordering. We adjusted for age group, sex, depression, dementia, rheumatoid arthritis, number of consultations (or encounters) with family physicians in two-year follow-up, number of comorbidities (defined as a sum of diabetes, osteoarthritis, hypertension, depression, dementia, Parkinson's disease, epilepsy, chronic obstructive pulmonary disease) and most recent body mass index (at the end of study follow-up in each cohort). Each family practice site was specified as a random effect in the regression model. The standardized proportion of TSH testing for each family practice was used to examine the heterogeneity in TSH testing in Canadian and English primary care population. In particular, an indirect standardization approach was used to standardize the proportion of TSH testing with respect to age range and sex (male, female) groups across family practices. Indirect standardization was carried out using the reference population structure of the

asymptomatic cohort in the CPCSSN and RCGP RSC databases. A funnel plot was constructed to examine the distribution of standardized proportion of patients with TSH test during study period with respect to practice size. Smaller practices with fewer than 100 TSH tests (with or without identified indications) in a two-year period were not included in the funnel plot. All statistical analyses were conducted using SAS software, V.9.4 M4 (SAS Institute).

Ethics and Consent:

The study was reviewed and approved by the University of Toronto's Research Ethics Board (REB). It also received a favourable opinion from the RCGP RSC study review panel. CPCSSN has received REB approval from each host university for all participating practice-based research networks. All participating primary care providers have provided written informed consent for the collection and analysis of their EMR data.

Results:

The national CPCSSN dataset contained medical information on 1,818,459 patients (as of June 30th, 2017) while the RCGP RSC dataset contained information on 2,383,113 patients (as of December 31st, 2017). The generation of the study cohorts is shown on Table 1. The study cohorts of patients with no identified indication for TSH testing included 489,663 patients in Canada (step 7 of table 1) and 1,030,489 (step 6 of table 1) patients in England.

There were 176,134 patients (35.97%) in the Canadian cohort and 302,504 patients (29.36%) in the English cohort that were tested for TSH at least once in the two-year observation period. Patient characteristics are shown in Table 2. In both cohorts, the proportion of patients tested for TSH was higher among patients in older age group; female patients; patients with diagnosis of depression, dementia, rheumatoid arthritis; patients with increasing number of co-morbidities and consultations. Patients with at least one TSH test had a mean of 1.30 tests done (228,907 tests for 176,134 patients) in Canada and 1.37 tests done (415,280 tests for 302,504 patients) in England during the two-year period studied. 95.69% of TSH tests were within the normal range (0.4-5.0 mU/L) in Canada and 99.23% were normal in England; the proportion of TSH tests within normal range remained the same with multiple testing within two-years. Around half of the TSH tests in Canada (51.40%) and three quarters in England (76.55%) were done on the same day as at least one of the screening tests we studied. The intracluster correlation for the outcome of TSH testing for patients nested within a family practice was 0.136 in the Canadian cohort and 0.062 in the English cohort.

Unadjusted odds ratios (ORs) are presented in supplementary Figure S1 and table S1 and adjusted ORs (AORs) in Figure 1 and supplementary table S2. Adjusted ORs for TSH testing was higher among older age group and female patients were more likely to get tested for TSH (AOR 1.75, 95% CI 1.72 to 1.77 in Canada and AOR 1.21, 95% CI 1.19 to 1.22 in England). The total number of consultations within the two-year observation period was the strongest predictor for TSH

testing in both asymptomatic cohorts; an increase in the total number of consultations or face-to-face visits to family practice was associated with a significantly higher proportion of patients with TSH tests.

Funnel plots for the proportion of patients in our cohorts with at least one TSH test by the size of the practice are shown in Figure 2. Only 34 out of 173 family practices (19.65%) were within three standard deviations of the mean for TSH testing in Canada and 41 out of 292 family practices (14.04%) in England. The wide dispersion reflects the lack of association between practice panel size and proportion of patients tested for TSH. Supplementary figure 2 presents the rank order of each practice with respect to the age and sex standardized proportion of patients tested for TSH in the last two years. The age and sex standardized proportion of patients per practice with at least one TSH test varied from 3.2% to 75.2 % across 173 practices in Canada and 9.5% to 56.4% across 292 practices in England.

Discussion

Approximately a third of adult patients with no identified indication for testing had at least one TSH test in a two-year period. Testing occurred on average more than once and most results were in the normal range. The strongest predictor of testing was a larger number of visits to the doctor. More than half of TSH tests were done on the same day as other common screening blood tests. While there was no correlation between size of the practice population and proportion of patients tested, there was wide variability in TSH ordering patterns by practice.

The findings of this study are consistent with an earlier retrospective chart review study on TSH test ordering, which found approximately one-quarter of tests did not conform to test-ordering guidelines.(14) Our study's bi-national sample supports these findings that a large volume of tests are being done for patients without identifiable indications. Our results are consistent with over-use: the incidence of thyroid dysfunction is 0.3% per year (26) and about one third of patients were tested in a two-year period; over 95% of TSH results were normal; most TSH tests were done with other screening laboratory tests; patients had more than one TSH done and these tests were normal again when repeated. A recent qualitative analysis found several possible reasons for the disparity in TSH ordering patterns in primary care, including lack of awareness of national policy changes.(27) We speculate that many TSH tests were done as part of routine screening or to reassure the patient or provider, in opposition to current recommendations.(4, 28)

There were areas of difference between Canada and England. In Canada, slightly more than half of TSH tests were bundled with other laboratory tests likely done for screening or chronic condition monitoring, such as a lipid profile or a hemoglobin A1c. In England, bundling occurred with three quarters of TSH tests. This difference of ~25% could relate to the test ordering interface in England that facilitates bundled order sets, rather than any actual distinction between clinical practice patterns related to TSH test ordering between the two countries. Specifically, in Canada tests are predominantly ordered individually on paper lab requisitions, while in England tests are ordered using electronic test ordering tools.

Regression analysis demonstrated that frequency of encounters was the strongest predictor of TSH testing. Further examination may point to opportunities to address TSH over-use for the population segment with frequent attendance. Our study also points to significant opportunities for health system improvements that support cost-effective care, given limited health care resources. A recent systematic review identified and critically appraised certain interventions to reduce ordering of thyroid function tests.(29) One example with increasing evidentiary support could be addressing provider screening habits such as routine bundling of TSH with other blood tests as part of preventive health exams. Recently, Wintemute et al demonstrated that an intervention for primary care groups comprised of education sessions on better test ordering, change management supports adapted to each groups unique context, and feeding back information on rates of TSH ordering over time compared to local peers was successful at reducing rates of unnecessary TSH tests in those settings.(15) Similar interventions could be replicated in other settings. Additionally, decreasing opportunities for lower value screening (for example, fewer preventive health exams for patients less likely to benefit) may also be helpful to reduce the overall number of inappropriately ordered TSH tests.(30)

While the data sources for this bi-national study reflect care routinely provided to patients in the two countries, there are some limitations of this study design, data sources and analytic methods. First, the study design does not allow us to infer causal relationships for possible over-testing for TSH. The findings of this study are limited to associations between patient characteristics and over-testing for TSH due to the possible existence of unmeasured confounding factors (e.g. unrecorded diagnosis of conditions related to thyroid test in EMR). In this study, the longitudinal data over two years of study follow-up was collapsed to a cross-sectional design. An alternative approach would be to consider time-dependent covariates relative to the date of TSH testing. However, this alternative approach was impractical due to sparse medical information available (especially among patients without TSH testing). Second, descriptive results are based on convenience sample of primary care practices that contribute EMR data to CPCSSN and RCGP RSC database. These practices may not be representative of all primary care providers even if their patient populations are representative. Third, our study assumes that TSH on its own is the only laboratory test being used to screen for thyroid disorders; however, there may be some clinical validity to screening using a TSH and a T4 test together to ensure that secondary hypothyroidism is not missed.(31) Our study does not include a population-level appropriateness evaluation of thyroid disorder screening using TSH and T4 together. Fourth, our databases do not include a complete evaluation of clinical documentation, specifically the narrative text which describes the clinical history and reasoning for ordering the test. As such, we may have overestimated the degree to which patient were asymptomatic at the time of TSH testing. Thus, it was

not feasible to determine the exact amount of TSH over-testing that occurred; rather we can only describe the patterns observed from the available data. Finally, due to inconsistent interfacing between electronic systems in different jurisdictions and with clinical specialists such as endocrinologists, it is possible that in small number of cases the study underestimates the true volume of TSH tests being ordered, or that some tests in the database were not ordered by the primary care providers but were counted as such. Future improvements to data quality of these databases could mitigate these possible sources for error if a study such as this one is replicated.

Conclusion

We found a high proportion of potentially unnecessary TSH tests in both Canada and England. There was significant variability in patterns of testing among different family practices; our results indicate the possibility of widespread use for screening purposes. The ability to use routine clinical EMR data to compare primary care delivered in two different countries supports using our findings as a benchmark to understand opportunities for improvements in several similar health systems and follow efforts to address over-use and improve allocation of limited health system resources. Implementation science approaches could be used to adopt larger initiatives to reduce lower value TSH testing, as recommended internationally by the Choosing Wisely campaign. Our data could be used for benchmarking to prospectively compare the effects of these efforts in different contexts and jurisdictions.

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Conflict of Interests

The authors have no competing interests to declare.
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Author contributions

MG initially conceptualized the study and wrote the first draft of the manuscript. NC led the writing of subsequent versions. SK led the analysis and presentation of the results, with contributions from WH, JS, JW, SdL, FS (England), CM, RM, BA, AS (Canada). These were reviewed and interpreted by all authors. All authors reviewed and revised the article for important intellectual content and gave final approval of the version to be published. MG is the guarantor of this paper and had final responsibility for the decision to submit for publication.

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Table 1: Cohort generation of patients in Canada and England

		Canada		England	
Step	**Description**	**Total number of patients**	**Percent drop with respect to previous step**	**Total number of patients**	**Percent drop with respect to previous step**
1	Total number of patients in the Canadian and UK databases as of December 31st 2017	1,818,459	-	2,383,113	-
2	patients excluded with no visit during the two years of study follow-up	1,117,870	38.5%	2,108,099	11.54%
3	patients excluded less than 18 years of age as of January 1st 2016	767,494	31.3%	1,670,832	20.74%
4	patients excluded with thyroid disease or on thyroid medication	680,610	11.3%	1,488,808	10.89%
5	patients excluded on lithium or amiodarone	676,517	0.60%	1,481,638	0.48%
6	Removing patients with other possible indications for thyroid testing (pregnancy, fatigue, weight gain, alopecia, galactorrhoea, insomnia, palpitations)	590,488	12.7%	1,030,489	30.45%

		Canada		England	
Step	**Description**	**Total number of patients**	**Percent drop with respect to previous step**	**Total number of patients**	**Percent drop with respect to previous step**
7	Removing patients not registered or assigned to a participating family physician in the national CPCSSN database	570,368	3.41%	-	-
8	Removing patients from CPCSSN networks that do not collect TSH data	530,342	7.02%	-	-
9	Removing providers who did not order any TSH test in the last two years	489,663	7.67%	-	-

Table 2: Proportion of patients with TSH test during observation period with respect to patient characteristics

	Canada			UK		
	Total number of patients	**N tested**	**Percent tested**	**Total number of patients**	**N tested**	**Percent tested**
Total number of patients	489663	176,134	35.97%	1030489	302,504	29.36%
Age group						
18-30 years	95390	22002	23.07%	195672	32593	16.66%
31-40 years	72408	20818	28.75%	164475	35378	21.51%
41-50 years	85254	31182	36.58%	202917	55088	27.15%
51-60 years	98379	38981	39.62%	183962	58358	31.72%
61-70 years	74288	32498	43.75%	151425	57408	37.91%
71-80 years	40517	19632	48.45%	91969	42717	46.45%
81+ years	23427	11021	47.04%	40069	20962	52.31%
Sex						
Missing	207	45	21.74%	-	-	-
Female	244596	103866	42.46%	453216	151483	33.42%
Male	244860	72223	29.50%	577273	151021	26.16%
Depression						
No	411019	140470	34.18%	843021	232572	27.59%
Yes	78644	35664	45.35%	187468	69932	37.30%
Dementia						
No	478525	170069	35.54%	998746	283958	28.43%
Yes	11138	6065	54.45%	31743	18546	58.43%

Rheumatoid Arthritis						
No	487328	175068	35.92%	1022414	299046	29.25%
Yes	2335	1066	45.65%	8075	3458	42.82%
Number of consultations during the two years						
1 to 4	210242	46651	22.19%	287520	23180	8.06%
5 to9	139990	55760	39.83%	250971	53674	21.39%
10 to 14	64981	32058	49.33%	163150	55243	33.86%
15 to 20	30884	16522	53.50%	105194	45412	43.17%
20+	43566	25143	57.71%	223654	124995	55.89%
No of comorbidities*						
0	261636	73725	28.18%	598544	116564	19.47%
1	136670	55905	40.91%	294305	107164	36.41%
2	62107	30307	48.80%	99560	53622	53.86%
3+	29250	16197	55.37%	38080	25154	66.06%
BMI range						
Missing	175380	40633	23.17%	128718	18411	14.30%
Underweight	5986	2476	41.36%	27876	6499	23.31%
Normal	97380	39526	40.59%	343404	92408	26.91%
Overweight	110544	46654	42.20%	320071	101917	31.84%
Obese class I	61182	27470	44.90%	139891	52796	37.74%
Obese class II	23899	11577	48.44%	47160	19937	42.28%
Obese class III	15292	7798	50.99%	23369	10536	45.09%
TSH test bundled**						
No		85606	48.60%		70936	23.45%
Yes		90528	51.40%		231568	76.55%

*defined as the sum of eight morbidities: chronic obstructive pulmonary disease, dementia, depression, diabetes, hypertension, osteoarthritis, Parkinson's disease, and epilepsy

**TSH test done on the same date as at least one other laboratory test commonly done for screening: Hemoglobin A1c, total cholesterol, triglyceride

Figure 1: Adjusted odds ratio for TSH testing

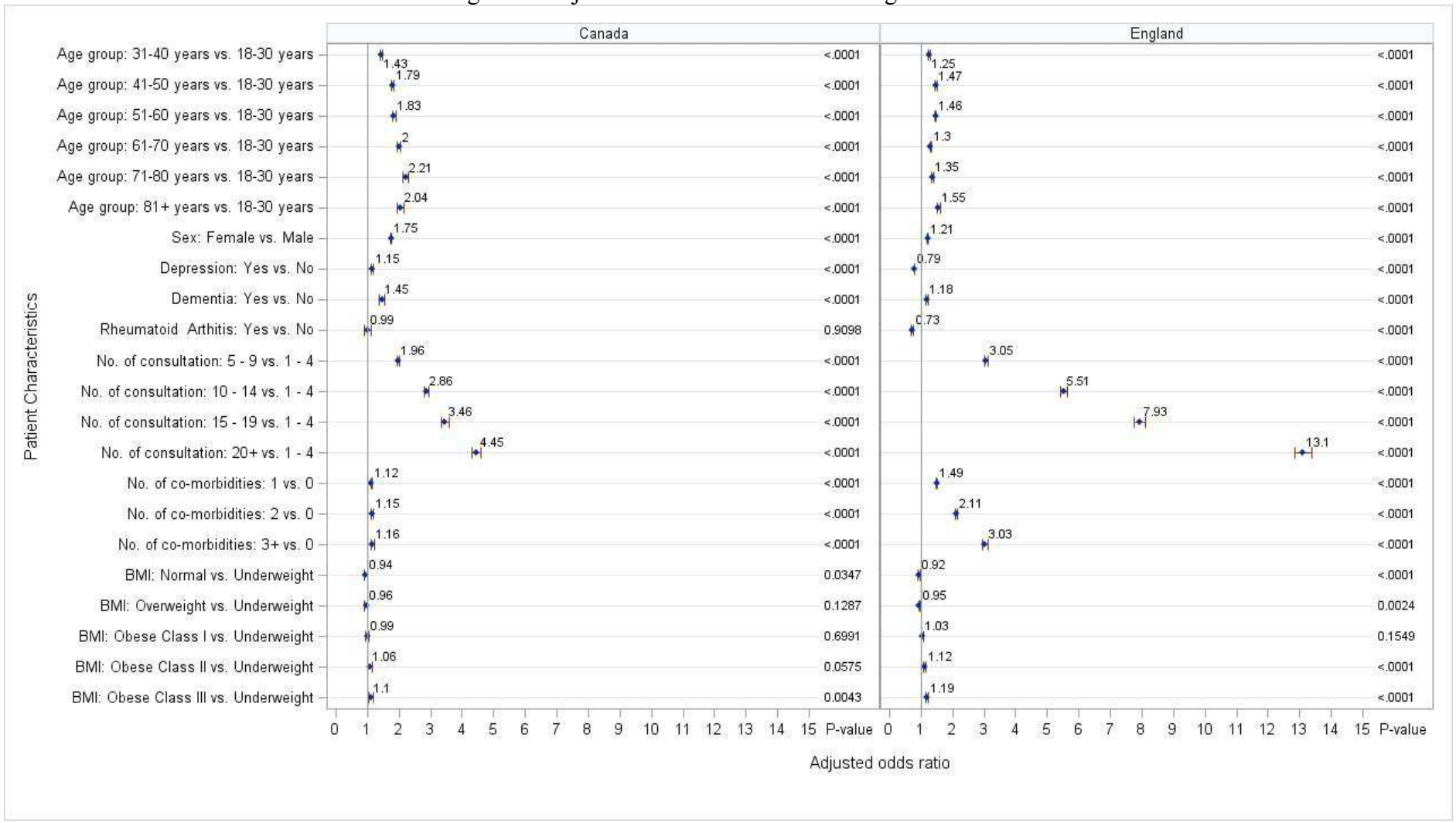

Figure 2: Funnel plot of proportion of patients with at least one TSH test (age and sex standardized) by number of patients in family practices