

# Older patients with hyperthyroidism have fewer symptoms as compared with younger patients

Boelaert K, Torlinska B, Holder RL, Franklyn JA. Older subjects with hyperthyroidism present with a paucity of symptoms and signs: a large cross-sectional study. *J Clin Endocrinol Metab* 2010. jc.2009- 2495 [pii];10.1210/jc.2009-2495 [doi]

## BACKGROUND

The diverse effects of hyperthyroidism are responsible for a wide variety of symptoms. These are related to the multiple effects of thyroid hormone that regulate energy and heat production, and facilitate the development of the central nervous system, somatic growth, puberty, and important hepatic, cardiac, neurologic, and muscular functions. Age plays a major role in the manifestations of hyperthyroidism, regardless of the underlying cause of the syndrome. Perhaps the most extreme example is the absence of symptoms in elderly patients who have apathetic thyrotoxicosis, a syndrome that can barely be recognized as hyperthyroidism. The objective of this study was to determine the prevalence of symptoms and signs of hyperthyroidism according to patient age and sex and the severity and type of hyperthyroidism.

## METHODS

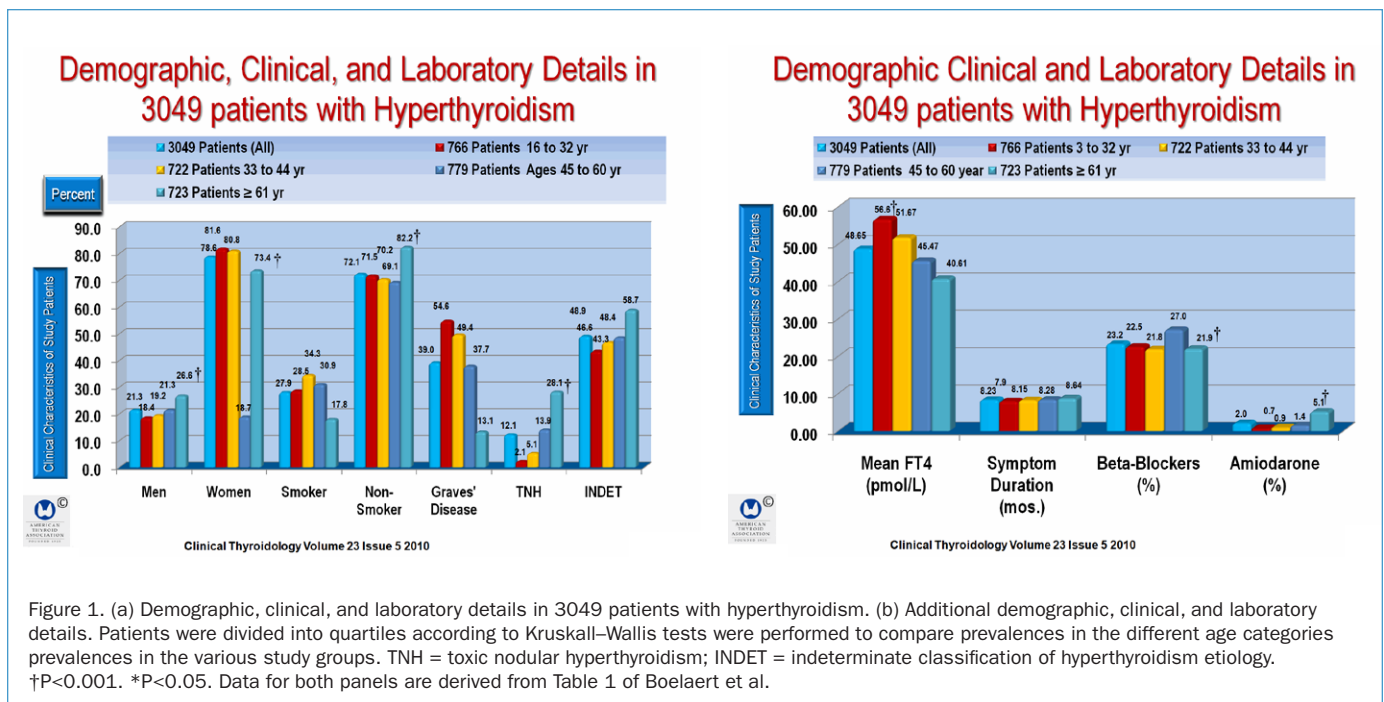
This is a cross-sectional study of 3049 consecutive patients with overt hyperthyroidism, the data from whom were collected from 1984 through September 2006 after presenting to the Multidisciplinary Thyroid Clinic, a secondary/tertiary referral center at the University Hospitals Birmingham. All patients were evaluated by a senior clinician at the time of presentation. A structured questionnaire was used for all patients throughout the study. Symptoms of thyroid ophthalmopathy were determined in patients with Graves' disease. All patients had a physical examination that recorded pulse rate and rhythm, the presence of tremor, and palpable goiter, with or without eye disease.

The diagnosis of hyperthyroidism was confirmed with measurements of serum free thyroxine (FT<sub>4</sub>), with or without a free triiodothyronine (FT<sub>3</sub>), and serum thyroxine (TSH). Thyroid-function tests were performed and thyroid antibody status was determined during the evaluation of symptoms and signs as described in a prior publication.

Ophthalmopathy was classified as no signs or symptoms; only signs without symptoms; signs only; proptosis; eye-muscle involvement; corneal involvement; sight visual acuity reduction (NOSPECS) score as previously described. Absent = (NOSPECS 0); 2 to 3 = periorbital edema/proptosis), 4 = severe NOSPECS, 4 to 6 = eye muscle involvement/corneal involvement/slight loss. The presence of atrial fibrillation was confirmed by electro-cardiography.

Patients were divided into quartiles according to age at the time of diagnosis: 766 were 16 to 32 years of age, 772 were 33 to 44, 779 were 45 to 60, and 732 were ≥61.

Patients were categorized into three diagnostic groups: Graves' disease, toxic nodular hyperthyroidism, and hyperthyroidism of indeterminate cause. Graves' disease was defined as biochemical hyperthyroidism and two of the following: a palpable diffuse goiter, a significant titer of thyroid peroxidase (>1:100), with or without thyroglobulin antibodies and with or without the presence of thyroid eye disease. Toxic nodular hyperthyroidism was defined as hyperthyroidism with a palpable nodular goiter. Patients who did not fulfill these criteria were categorized as indeterminate, thus representing a mixed group with Graves'



disease, toxic nodular hyperthyroidism, or both. Routine radionuclide imaging or thyroid-receptor antibody measurements were not performed. During follow-up, 28 patients were found to have transient hyperthyroidism due to subacute thyroiditis, and the analysis was thus repeated after exclusion of these patients. At the time of diagnosis, the patients' sex, age at diagnosis, and symptom duration were defined. Patients were classified as current smoker or nonsmoker, and a list of current medications, including  $\beta$ -blockers and amiodarone, were also identified.

**RESULTS**

**Clinical, Laboratory and Demographic Characteristics of the Patients (Figure 1)**

The study group comprised 2398 women (79%) and 650 men (21%), 16 through 88 years of age at the time of diagnosis (mean [±SD], 46.65±0.32). The ratio of women to men was lower in those 61 years or older as compared with younger patients. The rate of active smokers was lower in older patients. The highest rate of toxic nodular hyperthyroidism was in the oldest age group (≥61 years) as compared with younger patients, whereas younger patients had more severe hyperthyroidism at the time of diagnosis. The mean duration of symptoms at the time of diagnosis was similar across the age groups. The use of  $\beta$ -blockers was greatest in patients 45 to 60 years of age, but was similar when the youngest and oldest patients were compared (Figures 1A and 1B).

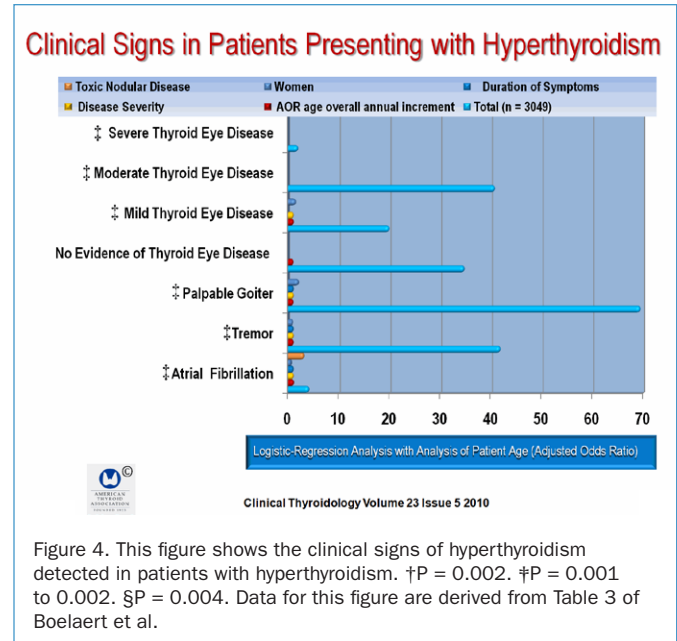
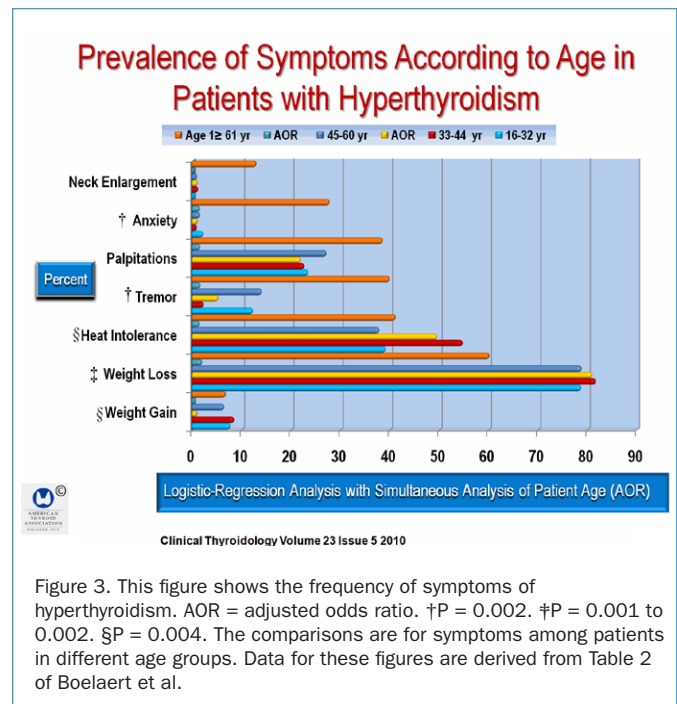
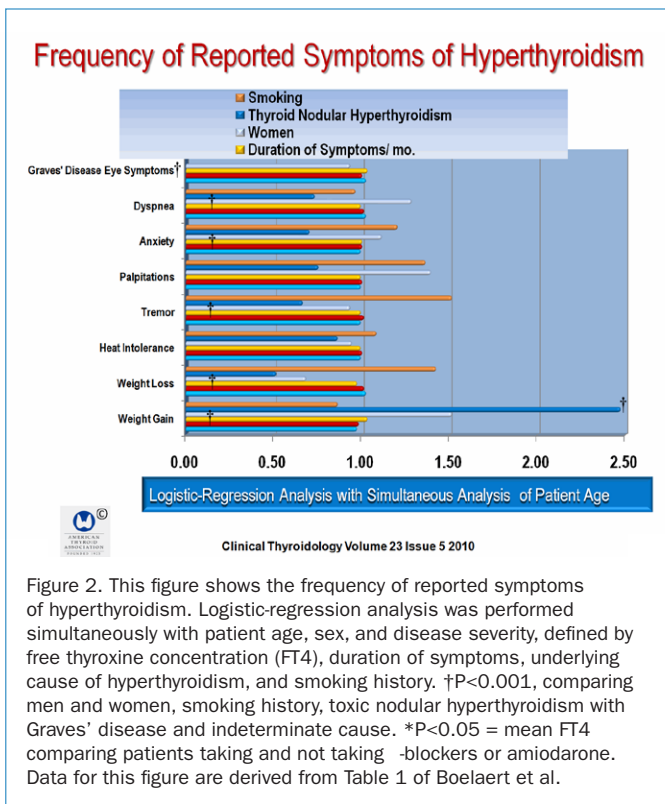
**Frequency of Reported Symptoms of Hyperthyroidism (Figures 2 and 3)**

The most common symptom was weight loss (60.7%), although 7.2% of the patients reported weight gain. About half the patients reported heat intolerance, tremor, and palpitations, and 41% reported anxiety (Figure 2). Eye symptoms were reported by 11.4% of the patients with Graves' disease.

Age 61 years or older was independently associated with reduced adjusted odds ratios (AORs) for the majority of symptoms, except for weight loss and dyspnea, which were more common in older patients as compared with younger patients (Figure 3). Symptoms of thyroid ophthalmopathy were more common in older than in younger patients with Graves' disease.

**Prevalence of Reported Signs of Hyperthyroidism According to Patient Age (Figures 3 and 4)**

Patients with more severe hyperthyroidism had significantly increased AORs for most of the classical symptoms of hyperthyroidism (Figures 3 and 4). However, patients with longer durations of symptoms were less likely to report weight loss, with the prevalence of other symptoms unaffected. Women were more



likely to report weight gain, palpitations, and neck enlargement; however, other symptom patterns were the same in men and women. There were few associations with the prevalence of classical symptoms. However, smoking was associated with increased AOR for weight loss, tremor, and anxiety as compared with nonsmokers. Women were more likely to report weight gain, palpitations, and neck enlargement (Figures 3 and 4).

After excluding 711 patients receiving  $\beta$ -blockers and 60 receiving amiodarone, the same regression analyses were performed. Still, the influence of age, disease severity, and smoking remained similar. However, patients receiving  $\beta$ -blockers were more likely to report weight loss [AOR, 1.50; 95% confidence interval, 1.23 to 1.83;  $P < 0.001$ ]. Evaluation of the number of reported symptoms in different age groups found that the highest proportion of patients with few symptoms—0, 1 or 2—were those 61 years or older (54.4%;  $P < 0.0001$ ), as compared with those 16 to 32 years of age (35.6%), 33 to 44 years (32.4%), and 45 to 60 years (29.8%) (Figures 5 and 6). The majority of patients older than 61 years of age reported a maximum of two symptoms, whereas the lowest fraction of patients reporting five or more symptoms was found among patients older than 61 years (Figure 5) Even after excluding those taking  $\beta$ -blockers or amiodarone, the number of symptoms of hyperthyroidism reported by patients was not substantially different.

**Influence of Demographic, Clinical and Laboratory Parameters (Figures 4 to 6)**

The mean pulse rate in the whole group was 84.4 beats/min, which was unchanged even after excluding those taking  $\beta$ -blockers or amiodarone. Although atrial fibrillation was found in 4.1% of the patients, it was independently associated with increasing age, more severe biochemical disease, and an underlying diagnosis of toxic nodular hyperthyroidism. Women were less likely to have atrial fibrillation, and neither smoking nor a longer duration of symptoms affected the presence of this arrhythmia (Figures 5 and 6). The findings were similar after exclusion of patients with subacute thyroiditis, and neither smoking nor a longer duration of symptoms, or  $\beta$ -blockers or amiodarone significantly affected

the presence of this arrhythmia (Figure 4). Tremor was found in 41.8% of patients, which was associated with more severe hyperthyroidism, a shorter duration of symptoms, and smoking. This association with tremor was no longer present when patients were treated with  $\beta$ -blockers or amiodarone.

**Prevalence of Reported Signs of Hyperthyroidism According to Patient Age (Figure 3)**

Palpable goiters were found in the majority of patients (69.8%), were more common in women, and were associated with younger age, more severe hyperthyroidism, were more common in women and with longer duration of symptoms and smoking, and were present in those not on  $\beta$ -blockers or amiodarone.

Thyroid eye disease was absent or mild in the majority of patients with Graves' disease, but only 1.9% had severe ophthalmopathy. Moderate to severe ophthalmopathy was more common in older patients, current smokers, women, and patients with a longer duration of disease (Figure 4). After excluding patients who were treated with  $\beta$ -blockers or amiodarone, more severe eye disease was found in women.

**Effects of Age on Clinical Signs of Hyperthyroidism (Figures 5 and 6)**

Patients 45 to 60 years of age or older had increased AORs for atrial fibrillation as compared with patients 16 to 32 years of age. Tremor was least common in patients 16 to 32 years of age. Tremors were least common in patients 33 to 44 years of age, but were not different when comparing older with younger age groups. Moderate or severe ophthalmopathy was more common in patients 45 to 60 years of age and those 61 years or older as compared with younger patients.

**CONCLUSION**

Older patients with hyperthyroidism have fewer symptoms as compared with younger patients. Physicians should have a low threshold for performing thyroid-function tests in patients 60 years of age or older, especially those with atrial fibrillation, weight loss, and dyspnea.

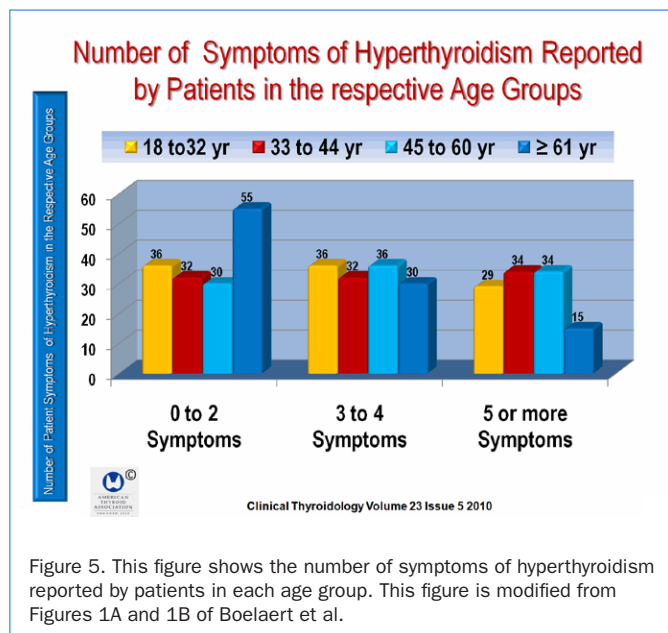


Figure 5. This figure shows the number of symptoms of hyperthyroidism reported by patients in each age group. This figure is modified from Figures 1A and 1B of Boelaert et al.

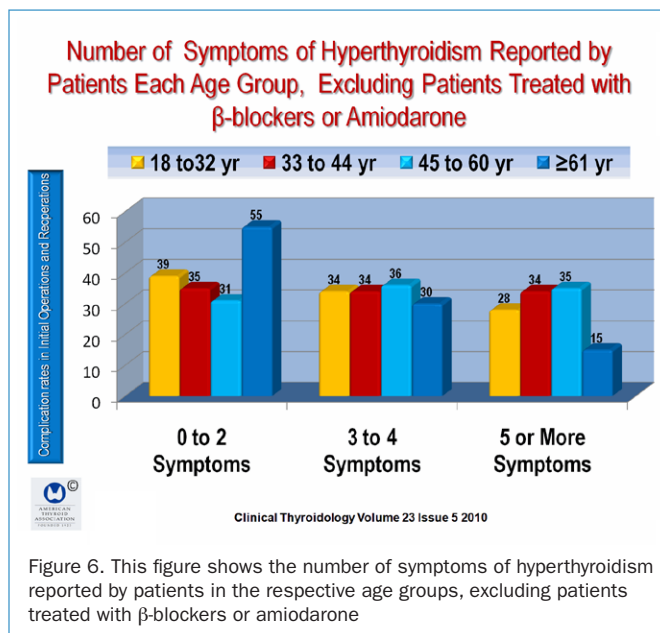


Figure 6. This figure shows the number of symptoms of hyperthyroidism reported by patients in the respective age groups, excluding patients treated with  $\beta$ -blockers or amiodarone

**COMMENTARY**

This is a large study of patients with hyperthyroidism that concurrently investigates the influence of age and a number of other clinical and biochemical features that affect the presenting symptoms and signs of hyperthyroidism. One of the main findings of this unique study is that more than 50% of the patients 61 years of age or older have very few symptoms of hyperthyroidism at the time of diagnosis. However, this occurs in only about 30% of younger patients with hyperthyroidism. Except for weight loss and shortness of breath, most of the usual symptoms of hyperthyroidism in older patients were independent of disease severity. Still, severe hyperthyroidism and current smoking were associated with AOR for most symptoms, while the patient's sex and the cause of hyperthyroidism affected the prevalence of symptoms in the majority of patients.

The risk of atrial fibrillation was increased in older patients, those with higher serum FT<sub>4</sub> concentrations, and men with toxic nodular hyperthyroidism. The signs of Graves' ophthalmopathy were more probable in older women, those with longer disease duration, and current smokers.

The authors opine that the strengths of this study are the large number of patients, the detailed evaluation of symptoms in a standardized manner, and the completeness of patient follow-up. On the other hand, they also acknowledge that the study has a few limitations, including the iodine-replete U.K. population under study, which may not be applicable to patients with different iodine uptake. Also, goiter was identified by physical examination and not routine neck ultrasonography. In addition, routine radionuclide scanning was not performed, because

treatment methods are similar for both Graves' disease and nodular hyperthyroidism. They also acknowledge that dyspnea in older patients might be partially due to underlying cardiovascular disease. And lastly, the authors recognize that patients may have been referred to a tertiary hospital after they were found to have abnormal thyroid function, thus producing some selection bias.

Previous studies by Boelaert et al and others (1,2) have found that advanced age is associated with less severe symptoms of Graves' hyperthyroidism and that there are age-related therapeutic responses to antithyroid drugs in patients with hyperthyroid Graves' disease (3). Boelaert et al. confirmed that older patients with Graves' disease have significantly lower serum FT<sub>4</sub> concentrations as compared with younger patients. Still, the cause for less severe Graves' hyperthyroidism in elderly patients remains uncertain. This study does demonstrate that patients with hyperthyroidism who are smokers are more likely to have weight loss, tremor, palpitations, and anxiety. The study also demonstrates that the severity of Graves' ophthalmopathy is associated with age and male sex (1) and underscores the clinical impact of smoking on the Graves' ophthalmopathy (4).

The study by Boelaert et al. confirms the effects of advancing age on the symptoms and signs of hyperthyroidism that may be readily missed on the initial evaluation, if the primary diagnosis is thought to be atrial fibrillation, dyspnea, or other cardiovascular problems (5, 6) and if this clinical concept is not kept in mind (4).

— Ernest L. Mazzaferri, MD, MACP

**References**

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