

AGE- AND SEX-SPECIFIC ASSOCIATIONS BETWEEN HASHIMOTO'S THYROIDITIS AND METABOLIC SYNDROME: A RETROSPECTIVE CLINICAL ANALYSIS

Stefanka Z. Kisova[✉], Maria M. Orbetzova, Dimitar M. Troev

Received on May 1, 2025

Presented by Ts. Tankova, Corresponding Member of BAS, on June 24, 2025

Abstract

Hashimoto's thyroiditis (HT) is the most common autoimmune thyroid disorder and is frequently associated with metabolic alterations. Metabolic syndrome (MetS), a constellation of metabolic abnormalities that increase cardiovascular risk, has been increasingly linked to thyroid dysfunction, especially in ageing populations. This study aims to evaluate the association between HT and MetS, with emphasis on age- and sex-related differences in a hospital-based cohort. A retrospective analysis was conducted on 499 patients diagnosed with HT at "St. George" University Hospital, Plovdiv, Bulgaria, between October 2019 and December 2021. Data included anthropometric measurements, thyroid hormone levels, lipid and glucose profiles, and the presence of MetS based on the Joint Interim Statement criteria. Patients were stratified by sex and by decade-based age groups. MetS was diagnosed in 64 out of 499 patients (12.8%), with highest prevalence in the 51–61 (39.1%) and 62–72 (29.7%) age groups. Females comprised 71.9% of MetS cases. A significant positive correlation between TSH and age ($p < 0.0001$) was observed. No significant sex difference in mean TSH levels was found. TSH levels tended to rise with advancing age, suggesting age-related hypothalamic-pituitary-thyroid axis modulation. The findings underscore the importance of evaluating MetS risk in patients with Hashimoto's thyroiditis, particularly in postmenopausal women. Age-related endocrine changes and autoimmune activity may synergistically elevate metabolic risk.

Key words: Hashimoto's thyroiditis, ageing, metabolic syndrome, TSH, sex differences

<https://doi.org/10.7546/CRABS.2025.12.17>

Introduction. Hashimoto's thyroiditis (HT), also referred to as chronic lymphocytic thyroiditis, is the most common autoimmune thyroid disease and a leading cause of hypothyroidism in iodine-sufficient regions. Characterized by gradual thyroid failure and lymphocytic infiltration of the gland, HT affects a significant proportion of adults, particularly women and older individuals. Although classically associated with elevated thyroid-stimulating hormone (TSH) and thyroid autoantibodies, HT is increasingly recognized as a systemic condition with metabolic consequences.

In parallel, metabolic syndrome (MetS) has emerged as a global public health concern. Defined by a constellation of interrelated metabolic abnormalities, including central obesity, hyperglycemia, dyslipidemia, and elevated blood pressure, MetS confers a heightened risk of cardiovascular disease and type 2 diabetes. The interplay between thyroid dysfunction and metabolic syndrome is of growing clinical interest, as thyroid hormones regulate numerous metabolic processes, including lipid and glucose metabolism, thermogenesis, and vascular tone.

Several studies suggest that individuals with overt or subclinical hypothyroidism, particularly those with autoimmune etiology, may be predisposed to components of MetS [1–3]. Furthermore, ageing is independently associated with both HT and MetS, complicating the clinical picture in older adults [4–6]. However, data on the age- and sex-specific distribution of MetS among patients with Hashimoto's thyroiditis remain limited, especially in Eastern European populations.

This study aims to investigate the prevalence and characteristics of MetS in patients with HT, with a particular focus on how these associations differ across age groups and between sexes. Understanding these relationships may support targeted screening strategies and personalized management for patients at highest cardiometabolic risk.

Materials and methods. This retrospective cross-sectional study included 499 consecutive adult patients diagnosed with Hashimoto's thyroiditis who attended the Endocrinology department at "St. George" University Hospital in Plovdiv between October 2019 and December 2021. All procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki and established Good Clinical Practice guidelines. The study was approved by the Ethics Committee of the Medical University – Plovdiv (protocol No. 5/24.04.2025). All participants met the established inclusion criteria. The diagnosis of HT was based on a combination of clinical features, positive thyroid autoantibodies (anti-Tg, anti-TPO, TRAb), characteristic ultrasound findings, and, when available, fine-needle aspiration biopsy (FNAB). During hospitalization, anthropometric, instrumental, and biochemical assessments were performed. Height and weight were measured in centimeters and kilograms, respectively. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Blood pressure was measured using a standardized protocol. Laboratory tests included fasting

blood glucose, lipid profile (total cholesterol, HDL-C, LDL-C, triglycerides), and thyroid function tests (TSH, fT4, fT3). All laboratory values were obtained from the hospital's central laboratory using standardized methods. Fasting blood samples were collected between 07:00 and 09:00 AM following standard pre-analytical procedures.

Reference ranges: TSH: 0.34–5.60 mIU/L; FT3: 3.8–6.0 pmol/L; FT4: 7.86–14.41 pmol/L; TC: 3.0–5.2 mmol/L; TG: 0.4–1.70 mmol/L; HDL: 1.03–1.6 mmol/L; FPG: 2.8–6.1 mmol/L.

Metabolic syndrome was defined using the Joint Interim Statement (JIS) criteria [5], requiring the presence of at least three of the following five components:

1. Waist circumference ≥ 94 cm for men or ≥ 80 cm for women;
2. Triglycerides ≥ 1.7 mmol/L or specific treatment for this lipid abnormality;
3. HDL-C < 1.0 mmol/L in men or < 1.3 mmol/L in women, or specific treatment;
4. Blood pressure $\geq 130/85$ mmHg or current use of antihypertensive medication;
5. Fasting plasma glucose ≥ 5.6 mmol/L or previously diagnosed type 2 diabetes.

Participants were stratified by sex and into six age categories: 18–28, 29–39, 40–50, 51–61, 62–72, and 73+ years. Descriptive statistics were presented as means and standard deviations for continuous variables and as frequencies and percentages for categorical variables. Group differences were assessed using *t*-tests and chi-square tests, as appropriate. Correlation analyses between age, TSH, and MetS parameters were performed using Pearson's correlation. A *p*-value < 0.05 was considered statistically significant. Data analysis was conducted using IBM SPSS Statistics version 19.0 (Chicago, IL, USA), and graphical presentations were created using Microsoft PowerPoint and Excel.

Results. Given the well-documented gender disparity in thyroid disorders, the distribution of cases by sex was closely examined. Of the 499 patients included in this study, 83.6% were women and 16.4% were men, reflecting a female-to-male ratio of approximately 5:1. This marked predominance among females aligns with previous epidemiological data and is further accentuated with increasing age.

All patients were stratified into six age groups by decade: 18–28, 29–39, 40–50, 51–61, 62–72, and 73 years and older (Fig. 1).

A one-sample *t*-test indicated no statistically significant difference in mean TSH levels between males and females ($p = 0.214$), suggesting that sex does not independently influence serum TSH concentrations in this cohort. In contrast, Pearson correlation analysis revealed a strong positive association between TSH and age ($r = 0.31$, $p < 0.0001$), highlighting the importance of age as a factor in thyroid function interpretation (Fig. 2).

Mean serum TSH levels demonstrated a progressive increase with advancing age, reaching the highest values in individuals aged 73 and above. This trend may

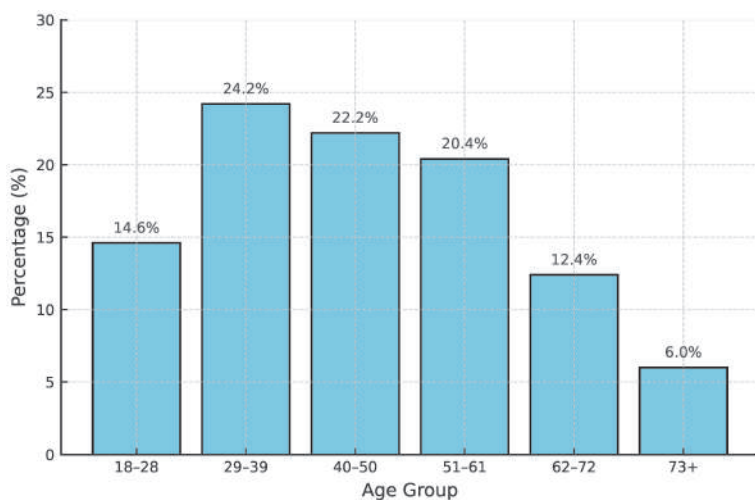


Fig. 1. Age distribution of participants

reflect physiological adaptations of the hypothalamic-pituitary-thyroid (HPT) axis to ageing, including diminished peripheral metabolism of thyroid hormones and altered feedback sensitivity.

Figure 2 shows the average TSH values for each age group, indicating a positive correlation with ageing.

In the present study, among the 499 patients diagnosed with Hashimoto's thyroiditis, 64 fulfilled the diagnostic criteria for metabolic syndrome (MetS). Of these, 71.9% were women and 28.1% were men (Table 1). Age-stratified analysis revealed a distinct pattern: the prevalence of MetS peaked in the 51–61 (39.1%)

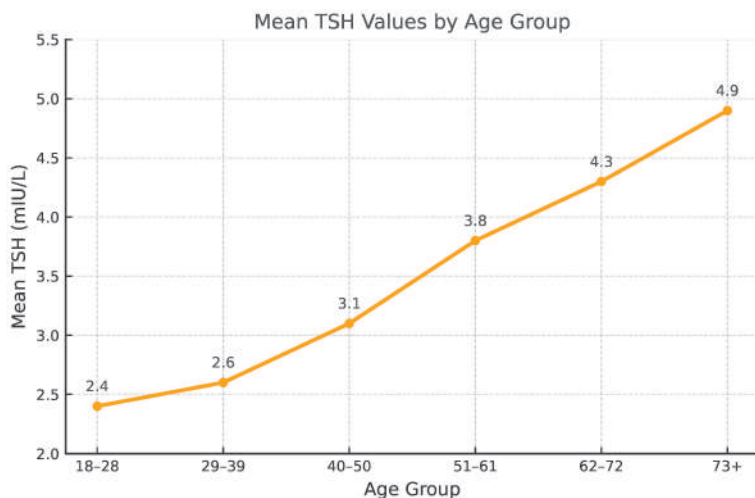


Fig. 2. Mean TSH values by age group

T a b l e 1

Distribution of MetS cases by sex ($n = 64/499$)

Sex	Number with MetS	Percentage
Male	18	28.1%
Female	46	71.9%
Total	64	100%

and 62–72 (29.7%) age groups. When evaluated according to individual MetS criteria – elevated triglycerides (> 1.7 mmol/L), reduced HDL-C (< 1.3 mmol/L), and hypertension – 46 of the 64 MetS cases were women, the majority of whom fell within the same two age groups (Fig. 3).

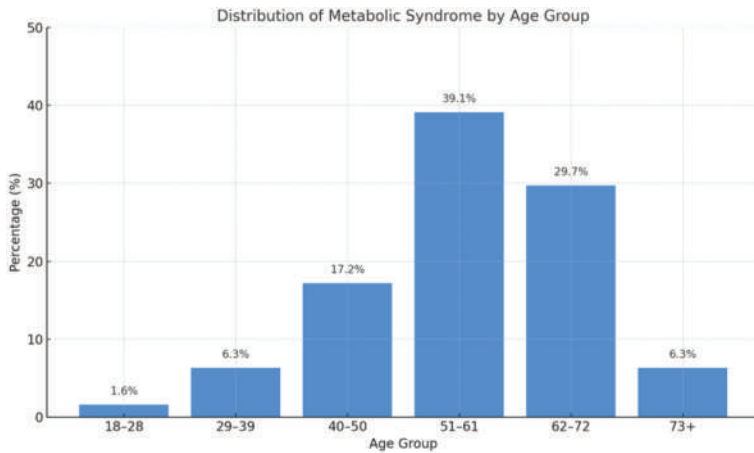


Fig. 3. Distribution of MetS cases by age groups

Notably, women aged 50 and older – presumably postmenopausal – exhibited a disproportionately higher prevalence of MetS compared to their male counterparts. This observation may reflect the combined impact of hormonal changes, autoimmune activity, and age-related metabolic dysregulation.

Figure 3 illustrates the percentage of patients with metabolic syndrome across different age groups.

Discussion. Thyroid hormones exert widespread effects on metabolic processes, including lipid and glucose metabolism, vascular tone, and energy expenditure. Consequently, thyroid dysfunction – particularly hypothyroidism – is an established risk factor for cardiovascular disease. Recent evidence suggests that elevated serum TSH levels are associated with unfavourable lipid profiles and other markers of metabolic disturbance [7].

The association between thyroid disorders and components of metabolic syndrome (MetS) has garnered increasing clinical interest due to their mutual links

with cardiovascular morbidity and mortality. Notably, both overt and subclinical hypothyroidism have been implicated in raising the risk of MetS. Furthermore, several studies have identified a correlation between higher TSH levels – even within the euthyroid range – and an increased prevalence of MetS. Specifically, TSH concentrations above 2.5 mIU/L have been linked to a higher risk of MetS, even in individuals without overt thyroid dysfunction [8]. In a study by RUHLA et al. [9], TSH levels below 2.5 mIU/L were associated with a more favourable metabolic profile. Similarly, OH et al. [10] suggested that healthy women with TSH levels exceeding 2.5 mIU/L should be screened for components of MetS. These findings support the hypothesis that subtle variations in thyroid function may significantly impact metabolic health, even in the absence of overt thyroid disease.

The American Cardiovascular Health Study, which followed 843 individuals with a mean age of 72 years over a 13-year period, reported a 13% increase in serum TSH levels, a 1.7% increase in FT4, and a 13% decrease in total T3 concentrations [11]. These longitudinal changes suggest a progressive shift in thyroid hormone metabolism with ageing. Supporting this, a cross-sectional study demonstrated that centenarians exhibited significantly higher mean TSH levels (1.97 mIU/L) compared to age-matched controls (1.55 mIU/L), further reinforcing the concept of an age-related adaptive mechanism in the hypothalamic-pituitary-thyroid axis [12].

Over recent decades, profound lifestyle transitions – including increased caloric intake and decreased physical activity – have contributed to the global surge in obesity, hyperglycemia, and hypertension, reaching epidemic proportions. According to World Health Organization (WHO) estimates, more than 1 billion adults are overweight, with approximately 890 million classified as obese. As a constellation of interrelated metabolic risk factors, metabolic syndrome (MetS) now affects over one-third of adults in the United States [13] and shows rising prevalence in low- and middle-income countries. MISRA and KHURANA [14] reported that MetS prevalence was 33.5% in Sub-Saharan Africa and the Middle East, 28.8% in India, 33.4% in Turkey, 33.7% in Iran, 31.2% in Venezuela, and 25.4% in Brazil. MetS is strongly linked to an elevated risk of type 2 diabetes and major cardiovascular events, including myocardial infarction, stroke, and heart failure.

In their global burden analysis, HUANG et al. [15] identified obesity and smoking as principal drivers of non-communicable diseases, with obesity alone accounting for over 363 000 deaths and 12.3 million years lived with disability.

Metabolic processes are influenced by sex-specific hormonal environments, contributing to differences in cardiometabolic risk between men and women. Pre-menopausal women typically exhibit lower central adiposity and are relatively protected from cardiovascular disease [16]. However, the transition to menopause marks a pivotal shift: declining estrogen levels promote redistribution of body fat toward a more central (android) pattern, akin to that observed in men [17]. While ovarian estrogen production diminishes significantly, adrenal androgen se-

cretion remains relatively unchanged. This hormonal shift likely contributes to the increased prevalence of MetS observed in postmenopausal women.

Menopause is associated with unfavourable changes in all core MetS components, including central obesity, elevated blood pressure, dyslipidemia, and insulin resistance. Moreover, the prognostic value of MetS for predicting cardiovascular outcomes and all-cause mortality appears to be greater in women than in men [18].

Thyroid disorders also exhibit marked sex differences. Autoimmune thyroid diseases, such as Hashimoto's thyroiditis, disproportionately affect women and become more common with advancing age. These trends are accompanied by a rightward shift in the serum TSH distribution curve. Importantly, both overt and subclinical thyroid dysfunction have been independently associated with increased risk of coronary artery disease and mortality [19], highlighting the importance of routine thyroid screening in older adults – particularly those with features of MetS.

Our findings support this evidence base, revealing a clear age-dependent increase in both MetS and thyroid dysfunction, especially among women over the age of 50. These observations underscore the need for targeted metabolic and endocrine evaluation in this high-risk subgroup.

Conclusion. The combined effect of age and sex on the interplay between thyroid dysfunction and metabolic syndrome (MetS) emerges as a key finding of this analysis. Women, particularly those over the age of 50, demonstrated a disproportionately higher risk of MetS in the context of elevated TSH levels. This likely reflects the diminishing cardioprotective influence of estrogen after menopause, compounded by a greater female susceptibility to autoimmune thyroid disease. The dual burden of hormonal decline and thyroid dysregulation may act synergistically to amplify cardiometabolic risk in postmenopausal women.

MetS and HT are among the most common endocrine conditions worldwide, sharing overlapping clinical features and pathophysiological mechanisms. Their combined impact on cardiovascular morbidity, diabetes incidence, and overall mortality represents a significant public health challenge.

These findings highlight the importance of early identification and integrated management strategies, particularly in ageing women with autoimmune thyroid disease. Regular metabolic screening and thyroid function assessment in this high-risk population may facilitate timely interventions and ultimately reduce the social, clinical, and economic burden of these interrelated disorders.

Study limitations.

1. Retrospective design limits the ability to infer causality.
2. Data are derived from a single clinical centre, potentially reducing generalizability.
3. Lifestyle factors (diet, physical activity, medications) were not included in the analysis.
4. Sex hormone levels (e.g., estrogen, testosterone) were not measured, which limits mechanistic interpretation.

Recommendations for future research.

- Conduct prospective, multicentre studies to explore causality and temporal trends.
- Include hormonal (estrogen/androgen) and inflammatory markers for a more comprehensive analysis.
- Assess the impact of thyroid hormone normalization on MetS outcomes.
- Develop age- and sex-specific screening protocols for at-risk populations.

REFERENCES

- [1] BIONDI B., D. S. COOPER (2008) The clinical significance of subclinical thyroid dysfunction, *Endocr. Rev.*, **29**(1), 76–131.
- [2] MARATOU E., D. J. HADJIDAKIS, M. PEPPA et al. (2010) Studies of insulin resistance in patients with clinical and subclinical hyperthyroidism, *Eur. J. Endocrinol.*, **163**(4), 625–630.
- [3] DíEZ J. J., P. IGLESIAS (2011) An analysis of the relative risk for components of the metabolic syndrome in patients with subclinical hypothyroidism, *Clin. Endocrinol. (Oxf)*, **75**(6), 792–797.
- [4] DUNTAS L. H. (2002) Thyroid disease and lipids, *Thyroid*, **12**(4), 287–293.
- [5] ALBERTI K. G. M. M., R. H. ECKEL, S. M. GRUNDY et al. (2009) Harmonizing the metabolic syndrome, *Circulation*, **120**(16), 1640–1645.
- [6] HOLLOWELL J. G., N. W. STAEHLING, W. D. FLANDERS et al. (2002) Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III), *J. Clin. Endocrinol. Metab.*, **87**(2), 489–499.
- [7] WARING A. C., N. RODONDI, S. HARRISON et al. (2012) Thyroid function and prevalent and incident metabolic syndrome in older adults: the Health, Ageing and Body Composition Study, *Clin. Endocrinol.*, **76**, 911–918.
- [8] ERDOGAN M., A. CANATAROGLU, S. GANIDAGLI et al. (2011) MetS prevalence in subclinical and overt hypothyroid patients and relation to MetS parameters, *J. Endocrinol. Invest.*, **34**, 488–492.
- [9] RUHLA S., M. O. WEICKERT, A. M. ARAFAT et al. (2010) A high normal TSH is associated with the metabolic syndrome, *Clin. Endocrinol.*, **72**, 696–701.
- [10] OH J. Y., Y. A. SUNG, H. J. LEE (2013) Elevated TSH is associated with metabolic syndrome in euthyroid young women, *Korean J. Intern. Med.*, **28**, 180–186.
- [11] SURKS M. I., J. G. HOLLOWELL (2007) Age-specific distribution and interpretation of serum thyrotropin values in older adults, *Thyroid*, **17**(6), 421–423.
- [12] ATZMON G., N. BARZILAI, J. G. HOLLOWELL et al. (2009) Extreme longevity is associated with increased serum thyrotropin, *J. Clin. Endocrinol. Metab.*, **94**(4), 1251–1254.
- [13] FORD E. S., C. LI, G. ZHAO (2010) Prevalence and correlates of metabolic syndrome based on a harmonious definition among adults in the US, *J. Diabetes*, **2**(3), 180–193.
- [14] MISRA A., L. KHURANA (2008) Obesity and the metabolic syndrome in developing countries, *J. Clin. Endocrinol. Metab.*, **93**, S9–S30.

- [15] HUANG C., H. YU, J. P. KOPLAN (2014) Can China diminish its burden of non-communicable diseases and injuries by promoting health in its policies, practices, and incentives?, *Lancet*, **384**(9945), 783–792.
- [16] VAN PELT R. E., C. M. JANKOWSKI, W. S. GOZANSKY et al. (2011) Sex differences in the association of thigh fat and metabolic risk in older adults, *Obesity*, **19**(2), 422–428.
- [17] PELLEGRINI M., V. PALLOTTINI, R. MARIN et al. (2014) Role of the sex hormone estrogen in the prevention of lipid disorder, *Curr. Med. Chem.*, **21**(24), 2734–2742.
- [18] REGITZ-ZAGROSEK V., E. LEHMKUHL, S. MAHMOODZADEH (2007) Gender aspects of the role of the metabolic syndrome as a risk factor for cardiovascular disease, *Gend. Med.*, **4**, Suppl. B, S162–S177.
- [19] FORD E. S. (2005) Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence, *Diabetes Care*, **28**(7), 1769–1778.

*Clinic of Endocrinology and Metabolic Diseases, “St. George” University Hospital,
66 Peshtersko Shosse Blvd, 4001 Plovdiv, Bulgaria*

and

*Department of Endocrinology, Faculty of Medicine, Medical University – Plovdiv,
15A Vassil Aprilov Blvd, 4002 Plovdiv, Bulgaria*

*e-mails: Stefanka.Kisova@phd.mu-plovdiv.bg, maria.orbetzova@mu-plovdiv.bg,
dimitar.troev@mu-plovdiv.bg*