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Relationship between metabolic syndrome and thyroid nodules in healthy Koreans

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A portion of these results were presented in abstract form at the 2013 Seoul International Congress of Endocrinology and Metabolism in Seoul, Korea.

Background/Aims: This study evaluated the relationship between thyroid nodules and metabolic syndrome (MS) and its components in apparently healthy Koreans.

Methods: We reviewed the records of 3,298 subjects with no noticeable symptoms who underwent thyroid ultrasound imaging as part of a routine check-up between July 2009 and June 2010; of these, 1,308 were excluded based upon predefined criteria. Among the remaining 1,990 patients, we examined the association between MS and its components and the incidence of thyroid nodules.

Results: Of the 1,990 subjects included in this study, 38.4% (n = 764) had thyroid nodules and 12.7% (n = 253) had MS. Female sex, older age, higher body mass index, larger waist circumference, higher glycated hemoglobin level, lower thyroid stimulating hormone level, and presence of MS were all closely related with the presence of thyroid nodules (all $p < 0.05$). Furthermore, the relevant number of MS components showed a positive linear correlation with the occurrence of thyroid nodules ($p < 0.001$). Evidence of MS alone was not independently associated with thyroid nodules after adjusting for sex and age in a multivariate binary logistic regression analysis; however, glycated hemoglobin for females and waist circumference for males, as well as both age and thyroid stimulating hormone for all patients, were identified as independent predictors for the existence of thyroid nodules (all $p < 0.05$).

Conclusions: This study suggests a positive relationship between the components of MS and thyroid nodules in an ostensibly healthy Korean population. Our data support the idea that the recent increase in thyroid nodules is partly due to increases in both MS and obesity.

Keywords: Thyroid nodule; Metabolic syndrome; Obesity

INTRODUCTION

The incidence of thyroid nodules and subsequent thyroid cancer has increased steadily over the last 30 years. Some of this increase may be due to advances in diagnostic tools, including high-resolution ultrasonography and computed tomography, allowing for greater detection of thyroid nodules, which may not have been detected before [1]; however, important changes in the intrinsic characteristics of the general population are also assumed to be involved [2].

Metabolic syndrome (MS) is characterized by a cluster of metabolic risk factors, including central obesity, hypertension, hyperglycemia, and dyslipidemia [3]. As modern industrialization has brought a nutritional surplus and sedentary lifestyles to the general popula-

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tion, the prevalence of MS has been rising exponentially worldwide. Recent data have demonstrated that MS is a risk factor not only for cardiovascular disease and diabetes [4] but also for tumors, including breast, colorectal, pancreatic, and prostate cancers [5-8].

Several previous studies have demonstrated positive associations between MS and thyroid nodules, both benign and malignant, in the general population in Western countries [9,10]. However, it is not known whether a similar association exists among Asian populations. Here, we designed a cross-sectional study to evaluate the relationship between thyroid nodules and MS and its components in ostensibly healthy Koreans.

METHODS

Study subjects

We retrospectively reviewed the records of all participants older than 18 years who underwent thyroid ultrasound exams as part of a routine medical check-up at the Health Promotion Center of Seoul St. Mary's Hospital, a major tertiary hospital in Seoul, Korea, from July 2009 to June 2010. Among the 3,298 asymptomatic subjects identified in our initial screen, we excluded subjects who had missing data in questionnaires; had a different racial or ethnic background; had a self-reported history of diabetes, cardiovascular, or thyroid disease; took lipid-lowering agents such as statins or omega-3 fatty acids; or showed abnormalities on thyroid function tests. Ethical approval for the study protocol and data analysis was obtained from the Institutional Review Board of Seoul St. Mary's Hospital.

Measurement of anthropometric and biochemical parameters

Height and weight were measured without shoes and while wearing light indoor clothes by trained healthcare personnel. Body mass index was calculated as weight divided by height squared (kg/m^2). Systolic and diastolic blood pressure readings were taken in a sitting position with an automatic device after a 10-minute rest. Waist circumference (WC) was measured at the level above the iliac crest, as defined by National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATPIII) guidelines [11].

Blood was drawn after an overnight fast. Fasting plasma glucose (FPG) levels were measured in serum with a modified glucose oxidase/peroxidase method (Sekisui Medical, Tokyo, Japan). Glycated hemoglobin (HbA1c) levels were measured with a G7 glycohemoglobin analyzer (Tosoh Bioscience, Tokyo, Japan). Total cholesterol (TC), triglycerides (TGs), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C) were determined using standard enzymatic methods (Sekisui Medical). Thyroid stimulating hormone (TSH) and free thyroxine were measured with an electrochemiluminescence immunoassay (Elecsys 1010, Roche, Indianapolis, IN, USA).

MS was defined as the condition in which three or more of the following metabolic components were satisfied, according to NCEP-ATPIII guidelines: (1) WC ≥ 90 cm in males, ≥ 80 cm in females; (2) TG ≥ 150 mg/dL; (3) HDL-C < 40 mg/dL in males, < 50 mg/dL in females; (4) blood pressure ≥ 130/85 mmHg or taking antihypertensive medication; and (5) FPG ≥ 100 mg/dL.

Thyroid evaluation

Thyroid ultrasonography was performed by radiologists using an HDI 5000 (Phillips Ultrasound, Bothell, WA, USA) with a 7-15 MHz transducer, according to the standard protocol of the health promotion center. The diagnosis of thyroid nodules was obtained from a review of radiological reports. A thyroid nodule was defined as discrete lesions distinct from the surrounding thyroid parenchyma, and which had a solid portion regardless of the presence of a cystic portion. The maximal diameter of a thyroid nodule was measured in three planes: longitudinal, transverse, and anteroposterior.

Statistical analysis

Categorical data are expressed as numbers and percentages of subjects. Continuous variables are expressed as the mean ± standard deviation. To evaluate differences in metabolic parameters between those with and without thyroid nodules, categorical variables were analyzed based on the chi-square test and continuous variables were compared with the unpaired *t* test. To find any association between metabolic components and the prevalence of thyroid nodules, we analyzed the data using a binary logistic regression analysis. A multivariate binary logistic regression analysis was used to determine independent factors for predicting the occurrence of thyroid nodules. A $p < 0.05$ was considered statistically significant. All analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Clinical characteristics of the study subjects

A total of 3,298 subjects were identified who underwent thyroid ultrasound exams as part of a general health check-up. Subjects were excluded from analysis based upon: (1) missing data in patient questionnaires (n = 156); (2) unknown race or ethnicity (n = 63); (3) known thyroid disease (n = 180); (4) use of lipid-lowering agents, including statins or omega-3 fatty acids (n = 279); (5) history of diabetes (n = 175) or cardiovascular disease (n = 123); or (6) thyroid dysfunction (n = 332) (Fig. 1). Based upon these criteria, we were able to identify 1,990 subjects for inclusion in the final study population.

Metabolic variables and thyroid nodules

The baseline characteristics of the study subjects are summarized in Tables 1 and 2. Among the 1,990 subjects in the final analysis, 764 (38.4%) had thyroid nodules and 253 (12.7%) had MS. The study population consisted of 1,299 females (65.3%) and had a mean age of 49.8 ± 10.0 years.

Subjects with thyroid nodules showed a higher female to male ratio (70.8% vs. 61.8%, $p < 0.001$) and older age (52.4 ± 9.5 years vs. 48.2 ± 10.0 years, $p < 0.001$) relative

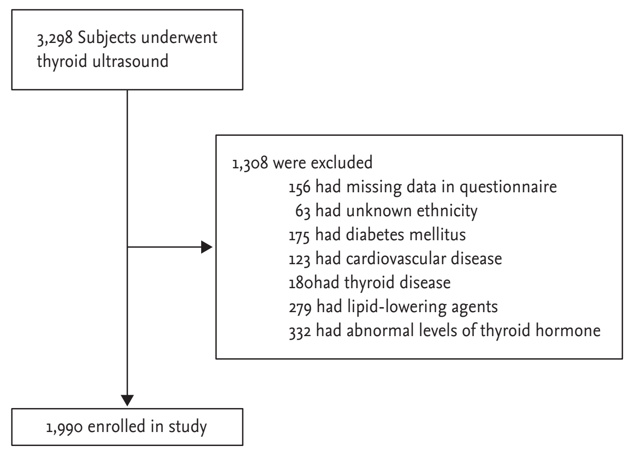

Figure 1. Selection of study participants.

Table 1. Metabolic variables and presence of thyroid nodules in subjects with and without thyroid nodules

Variable	Total (n = 1,990)	With thyroid nodule (n = 764)	Without thyroid nodule (n = 1,226)	p value[a]
Male sex	691 (34.7)	223 (29.2)	468 (38.2)	< 0.001
Age, yr	49.8 ± 10.0	52.4 ± 9.5	48.2 ± 10.0	< 0.001
Systolic blood pressure, mmHg	118.4 ± 14.3	119.2± 14.3	118.0 ± 14.3	0.073
Diastolic blood pressure, mmHg	69.2 ± 10.1	69.5± 10.2	69.0 ± 10.1	0.279
Body mass index, kg/m^2	22.9 ± 3.1	23.2 ± 3.0	22.7 ± 3.1	0.001
Waist circumference, cm	82.3 ± 8.1	83.2± 8.1	81.8 ± 8.1	< 0.001
Fasting plasma glucose, mg/dL	87.0 ± 15.2	87.7 ± 16.3	86.5 ± 14.5	0.083
Glycated hemoglobin, %	5.5 ± 0.5	5.6 ± 0.6	5.5 ± 0.5	< 0.001
Total cholesterol, mg/dL	199.2 ± 34.1	199.6 ± 33.9	198.9 ± 34.3	0.644
Triglyceride, mg/dL	93.7 ± 66.2	94.6 ± 59.0	93.1 ± 70.3	0.619
HDL-C, mg/dL	55.2 ± 13.1	54.8 ± 12.6	55.5 ± 13.4	0.253
LDL-C, mg/dL	120.0 ± 31.1	120.3 ± 31.1	119.8 ± 31.1	0.757
TSH, mIU/L	2.1 ± 1.1	2.0 ± 1.0	2.2 ± 1.1	< 0.001
Free thyroxine, ng/dL	1.3 ± 0.2	1.3 ± 0.2	1.3 ± 0.2	0.883
Metabolic syndrome	253 (12.7)	115 (15.1)	138 (11.3)	0.015

Values are presented as number (%) or mean ± SD.
HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TSH, thyroid stimulating hormone.
[a]With thyroid nodule vs. without thyroid nodule.

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Table 2. Metabolic variables and presence of thyroid nodules in subjects with and without metabolic syndrome

Variable	Total (n = 1,990)	With metabolic syndrome (n = 253)	Without metabolic syndrome (n = 1,737)	*p* value[a]
Male sex	691 (34.7)	109 (43.1)	582 (33.5)	0.004
Age, yr	49.8 ± 10.0	54.9 ± 9.0	49.1 ± 9.9	0.058
Systolic blood pressure, mmHg	118.4 ± 14.3	129.8 ± 15.5	116.8 ± 13.3	< 0.001
Diastolic blood pressure, mmHg	69.2 ± 10.1	76.3 ± 10.2	68.1 ± 9.7	< 0.001
Body mass index, kg/m^2	22.9 ± 3.1	25.8 ± 2.8	22.5 ± 2.9	< 0.001
Waist circumference, cm	82.3 ± 8.1	90.3 ± 6.9	81.2 ± 7.6	< 0.001
Fasting plasma glucose, mg/dL	87.0 ± 15.2	98.9 ± 26.2	85.2 ± 11.8	< 0.001
Glycated hemoglobin, %	5.5 ± 0.5	6.0 ± 0.9	5.5 ± 0.4	< 0.001
Total cholesterol, mg/dL	199.2 ± 34.1	208.3 ± 39.5	197.8 ± 33.1	< 0.001
Triglyceride, mg/dL	93.7 ± 66.2	173.8 ± 102.4	82.1 ± 49.3	< 0.001
HDL-C, mg/dL	55.2 ± 13.1	42.8 ± 8.8	57.0 ± 12.6	< 0.001
LDL-C, mg/dL	120.0 ± 31.1	128.3 ± 36.0	118.8 ± 30.1	< 0.001
TSH, mIU/L	2.1 ± 1.1	2.2 ± 1.1	2.1 ± 1.1	0.497
Free thyroxine, ng/dL	1.3 ± 0.2	1.3 ± 0.2	1.3 ± 0.2	0.592
Thyroid nodule	764 (38.4)	115 (45.5)	649 (37.4)	0.015
Thyroid nodule size ≥ 1 cm	186/764 (24.3)	38/115 (33.0)	148/649 (22.8)	0.002
Thyroid nodule multiplicity	297/764 (38.9)	49/115 (42.6)	248/649 (38.2)	0.346

Values are presented as number (%) or mean ± SD.
HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TSH, thyroid stimulating hormone.
[a]With metabolic syndrome vs. without metabolic syndrome.

Table 3. Multivariate binary logistic regression analysis of independent predictors for the presence of thyroid nodules (n = 1,635)

Variable	Odds ratio	*p* value
Female sex (n = 1,140)		
Age, yr	1.059	< 0.001
Systolic blood pressure, mmHg	0.989	0.151
Diastolic blood pressure, mmHg	1.005	0.635
Waist circumference, cm	1.011	0.283
Glycated hemoglobin, %	1.512	0.011
Triglyceride, mg/dL	0.999	0.245
HDL-C, mg/dL	0.995	0.360
TSH, mIU/L	0.828	0.001
Male sex (n = 595)		
Age, yr	1.042	< 0.001
Systolic blood pressure, mmHg	0.989	0.352
Diastolic blood pressure, mmHg	1.005	0.741
Waist circumference, cm	1.042	0.005
Glycated hemoglobin, %	0.951	0.734
Triglyceride, mg/dL	1.000	0.780
HDL-C, mg/dL	0.999	0.882
TSH, mIU/L	0.714	< 0.001

HDL-C, high density lipoprotein cholesterol; TSH, thyroid stimulating hormone.

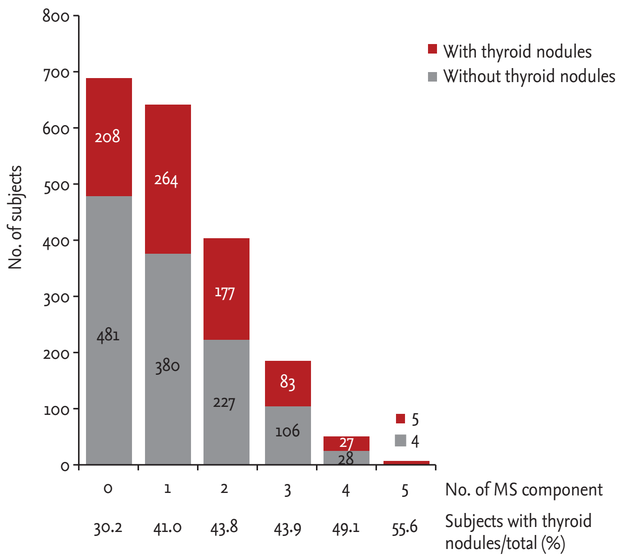

Figure 2. Association between the number of relevant components of metabolic syndrome (MS) and prevalence of thyroid nodules.

to those without thyroid nodules. The prevalence of MS was also higher in subjects with thyroid nodules than in those without (115/764 [15.1%] vs. 138/1,226 [11.3%], p = 0.015). Body mass index, WC, and HbA1c were significantly higher in subjects with thyroid nodules, while blood pressure, FPG, and lipid profiles, including TC, TG, HDL-C, and LDL-C, showed no statistically significant difference between groups. Subjects with MS had a higher prevalence of not only thyroid nodules but also nodules larger than 1 cm (Table 2). However, the prevalence of multiple thyroid nodules did not differ between subjects with or without MS.

Subjects with MS showed a lower female to male ratio (56.9% vs. 66.5%, p = 0.004) and a higher prevalence of thyroid nodules (45.5% vs. 37.4%, p = 0.015) than those without MS. The mean age of the subjects with MS was higher, though this difference was not statistically significant (54.9 ± 9.0 years vs. 49.1 ± 9.9 years, p = 0.058).

As the number of MS components satisfied increased, the proportion of patients with thyroid nodules rose, indicating a strong correlation between MS and thyroid nodules (β = 1.235, p < 0.001) (Fig. 2). However, individual components of MS did not show independent relationships with thyroid nodules after adjusting for sex and age. Moreover, age stratification showed that the prevalence of both thyroid nodules and MS was closely associated with age (Supplementary Fig. 1). To address these apparent discrepancies, we ran a multivariate binary logistic regression analysis to identify clinical variables that could independently predict the existence of thyroid nodules (Table 3). HbA1c levels were a significant predictor of thyroid nodules in females (p = 0.011), while WC was a significant predictor only in males (p = 0.005); higher age and lower TSH were significant factors for predicting thyroid nodules in both sexes (p < 0.001).

DISCUSSION

In this study, we explored the relationship between the presence of thyroid nodules and the components of MS in ostensibly healthy Koreans with no evidence of iodine insufficiency [12]. Our results suggest an association between thyroid nodules and MS components even in healthy populations, which may have important implications for the diagnosis and treatment of thyroid-related diseases.

MS is closely associated with an increase in overall mortality, due not only to increases in cardiovascular complications [4], but also malignant diseases [5-8]. Insulin resistance, a characteristic manifestation of MS, increases glucose and insulin levels, which stimulate cell proliferation. Large population studies revealed that patients with glucose metabolism disorders have a higher chance of both malignancy and mortality [5,13-16]. The tumorigenic effects of MS appear to be mediated through changes in cytokine levels, resulting in decreased expression of tumor suppression genes, and increases in oncogene expression due to inflammation and reactive oxygen species generation; other factors, such as the stimulation of angiogenesis and invasion of malignant cells into normal tissues, may also play a role [5]. While many of the mechanisms underlying these effects remain poorly understood, these activities are well supported by a variety of observational and laboratory studies.

Recent studies suggest that components of MS are possible risk factors for thyroid nodules, beyond many of the well-established ones, including sex, goiter, family history of thyroid cancer, and radiation exposure. MS is thought to trigger thyroid nodules via the stimulation of thyroid proliferation and angiogenesis brought on by hyperinsulinemia, hyperglycemia, and dyslipidemia [17-

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19]. Our data demonstrate that people with MS had a higher prevalence of thyroid nodules. The subjects with MS also had a higher prevalence of thyroid nodules larger than 1 cm, consistent with a previous study showing a positive association between insulin resistance and thyroid nodule size [19]. Furthermore, we showed that the number of accompanying MS factors had a significant positive correlation with the prevalence of thyroid nodules; the more components of MS were observed, the higher the chance of thyroid nodules. The prevalence of thyroid nodules may be affected by sex [20,21]; as older age was also positively correlated with not only the presence of thyroid nodules, but also MS [22], we analyzed the role of sex independently using multivariate logistic regression. After adjusting for age, higher HbA1c in females and larger WC in males were found to be significant factors for the presence of thyroid nodules.

Many previous studies have shown that hyperglycemia has a strong correlation with thyroid cancer in both sexes [23,24]. Our study demonstrates that hyperglycemia, as indicated by HbA1c levels, showed a significant relationship with the presence of thyroid nodules in women. An interesting finding is that HbA1c levels showed a significant association with thyroid nodules both before and after adjustment for related factors, whereas FPG levels did not. The exclusion of all known diabetic patients to target a metabolically normal population might make these two hyperglycemia-related parameters contradictory. Consistent with our study, a previous univariate analysis of an Icelandic cohort showed the relative risk for women with high 90-minute postprandial glucose levels for thyroid cancer was 1.12 [14], indicating that postprandial glucose levels may be associated with thyroid nodules and, potentially, thyroid cancer. Although the effects of postprandial hyperglycemia on tumor formation have been not well evaluated, hyperglycemia, oxidative stress, endothelial dysfunction, and the formation of advanced glycation end products may all potentially be involved in the pathophysiology of tumor formation [5,25,26]. As HbA1c levels are routinely used to screen for the existence of diabetes [27-30], our center was able to measure these levels across all patients; however, we were unable to evaluate insulin resistance outcomes, such as homeostasis model assessment of insulin resistance, as neither insulin nor c-peptide were routinely measured.

Anthropometric measurements showed inconsistent associations with the prevalence of thyroid cancer. Most studies that have evaluated the relationship between body mass index and thyroid cancer have reported a strong association between them [14,31,32]; however, the significance varied with sex. Kitahara et al. [33] demonstrated a slightly stronger association of WC and weight change with thyroid cancer risk in men versus women, which may be due to a difference in hormone profiles, such as leptin and estrogen, and the metabolic consequences of excess body fat in men and women.

TSH levels were inversely related with thyroid nodules, even though both TSH levels were within normal ranges. One possible explanation is that multiple thyroid nodules could maintain TSH levels at a lower normal range by autonomous hyperfunctioning. TSH has been shown to be suppressed in patients with a multinodular goiter [34], while TSH levels < 2.5 mIU/L may be related to an increased risk of MS [35]. These associations were not replicated in our study, with MS patients showing no increases in TSH levels (Table 2). This difference may be an artifact of the study design, as our study population consisted entirely of patients who underwent thyroid ultrasound imaging.

Our study has several unique clinical features. The most important aspect of this study is its use of clinically healthy subjects. Because we initially excluded all subjects with a history of diabetes or cardiovascular disease and those taking lipid-lowering agents, the prevalence of MS (12.7%) in our study population was much lower than that in the general Korean population, with MS prevalence rates estimated at 31.3% [36]. Although the strict inclusion criteria may have underestimated the effects of abnormal glucose and lipid metabolism on the thyroid, MS components showed significant connections with thyroid nodules. Second, this analysis was based on reliable parameters measured by specialists using standardized methods at a single center. The large number of subjects enrolled is also an important strength of this study.

Despite its many strengths, this study is not without limitations. First, it was a retrospective, cross-sectional study. Therefore, the study population might be biased, as the study population consisted of people who determined by themselves whether they should undergo thyroid ultrasonography. This aspect of the study design may explain why the prevalence of thyroid nodules was similar between sexes, unlike a previous study [21]. A longitudinal cohort study with a more representative population will be needed to address these potential issues. Second, we could not evaluate the association between insulin resistance and thyroid nodules because insulin and C-peptide levels were not available. A lack of cytological or histological results for each nodule is an important limitation. Future studies focusing on more biopsy-proven reports and with a longer follow-up duration will be necessary to provide a more complete and accurate evaluation of the relationship.

This study suggests an association between the components of MS and thyroid nodules in a healthy Korean population. Our data show that female sex, older age, lower TSH, and higher number of accompanying MS components were all positively associated with the presence of thyroid nodules. Future studies evaluating the effects of active interventions, including lifestyle modification and medication adjustments, on components of MS with regard to the incidence of thyroid nodules and, ultimately, the prevention of thyroid cancer, are therefore warranted.

KEY MESSAGE

1. There is a positive relationship between the components of metabolic syndrome (MS) and thyroid nodules in an ostensibly healthy Korean population.
2. A recent increase in thyroid nodules is partly due to increases in both MS and obesity.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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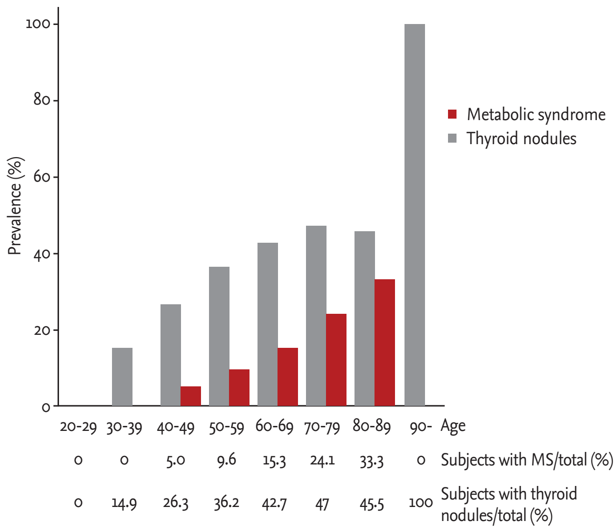

Supplementary Figure 1. Association between age and the prevalence of metabolic syndrome (MS) and thyroid nodules.