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# Factors Associated with Nodular Goiter in the General Population

**Master Thesis**
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Kaunas, Lithuania 2022

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# 1. ABSTRACT

***Author:*** Esraa Abdalla Abdalkarim Eltom

***Title:*** Factors associated with nodular goiter (NG) in the general population

***Aim****:* To conduct a systematic review of factors associated with NG in the general population.

***Objectives:*** 1. To determine prevalence of NG amongst general populations. 2. To determine the associations of modifiable and non-modifiable factors with NG. 3. To determine which factors independently increase NG risk in different populations. 4. To determine which factors play a role in malignancy development in individuals with NG.

***Methods:*** An electronic database search for studies was conducted. Initially, articles were screened by reading the title & abstract and excluded based on relevance. Full texts of remaining articles were then retrieved and assessed for eligibility using the inclusion & exclusion criteria. 27 articles were included.

***Results:*** Independent TN factors are: age, female sex, BMI, thyroid volume, higher TSH levels, smoking habits, metabolic syndrome (MetS), waist circumference (WC), elevated systolic blood pressure (SBP), increased fasting glucose (IFG), higher education, physical labour and milk consumption ($p < 0.05$). HDL was found to be a protective factor. Independent risk factors of goiter ($p < 0.05$) are: nodules, low TSH, female sex, BMI, smoking, MetS, WC, SBP, abdominal adiposity, hypertriglyceridemia and diabetes.

Of the 44,219 NG subjects assessed, independent factors were: age (OR 1.05-12), female sex (OR 1.91), BMI (OR 1.51), parity (OR 1.98), MetS (OR 1.34), low HDL (OR 2.77), impaired FPG (OR 2.23), previous & current smoking (OR 1.65, OR 1.31). Risk is increased by exposure to hydroxylated PAHs (OR 2.86-3.11), higher UBC levels (OR 6.15) and excess iodine (OR 4.93). Elevated TG serum levels (>60ng/ml) and low dietary iodine (60 $\mu$g/d $\pm$ 30) were associated with NNG in Israeli adults. In Turkey, euthyroid NG subjects have a higher PWV that is positively correlated with fasting glucose and WC ($p < 0.001$). In PCOS patients; older age, BMI, IFG and insulin are risk factors for both TN and TV ($p < 0.05$). Metformin therapy reduces benign NG risk in T2DM (hazard ratio: 0.527).

From the 2,854 MNG patients included, independent factors were: age (OR 1.049), female sex (OR 1.881), BMI (OR 1.507), parity (OR 1.648), smoking (OR 1.454), MetS (OR 1.409-1.87), abnormal glucose metabolism (OR 1.435), abdominal adiposity (OR 1.551) and SBP (OR 1.01). Alcohol reduces risk ($p < 0.05$) of TNs, NG & MNG.

In MNG patients, predictors of malignancy are: younger age, male sex, preoperative impression of malignancy, fewer nodules, smaller nodule, thyroid gland and adenoma size, histological thyroiditis, Hashimoto's thyroiditis, and CNST. Female gender and functional thyroid status decrease risk.

***Conclusion:*** In addition to nonmodifiable factors, lifestyle factors such as smoking, insulin resistance, MetS and its components play important roles in the development of NG. Future prospective studies, with large randomised study populations and longer follow-up periods should be carried out to strengthen the findings on the relationship between the disease, its contributing factors & malignancy.

## 2. ACKNOWLEDGEMENT

I would like to thank my supervisor Professor Birutė Žilaitienė, and my family, especially my sister Shiraz Eltom for all their support and guidance throughout the process of writing this systematic review.

## 3. CONFLICTS OF INTEREST

The author reports no conflicts of interest.

# 4. ETHICS COMMITTEE APPROVAL

Approved by: LSMU Bioethics center

Biomedical research name: Factors associated with Nodular Goiter in the general population

Number: BEC-MF-462

Date: 13/05/2022

# 5. ABBREVIATIONS

AITD: Autoimmune thyroid disease

AMPK/mTOR: AMP-activated protein kinase/mammalian target of rapamycin

BMI: Body mass index

BPA: Bisphenol A

CNST: Chronic non-specific thyroiditis

Cyclic AMP: Cyclic adenosine monophosphate

EGF: Epidermal growth factor

FPG: Fasting plasma glucose

HDL: High density lipoprotein

HT: Hashimoto's thyroiditis

IFG: Increased fasting glucose

IGF1: Insulin-like growth factor-1

IR: Insulin resistance

MetS: Metabolic Syndrome

MNG: Multinodular goiter

N/A: Not applicable

NCEP-ATP III: National Cholesterol Education Program-Adult Treatment Panel III

NG: Nodular goiter

NNG- Nontoxic Nodular goiter

OR (95% Cl): Odds ratio (95% Confidence Level)

PAH: Polycyclic aromatic hydrocarbons

PCOS: Polycystic ovary syndrome

PTC: Papillary thyroid carcinoma

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PWA: Pulse wave analysis

SHO: Subclinical hypothyroidism

SNG: Simple nodular goiter

STN: Solitary thyroid nodules

TN: Thyroid Nodules

TNG: Toxic nodular goiter

TSH: Thyroid stimulating hormone

TPO Ab: Thyroid peroxidase antibodies

TV: Thyroid Volume

T2DM: Type 2 diabetes mellitus

UBC: Urinary BPA concentrations

US: Ultrasonography

UIC: Urinary Iodine Concentrations

WC: Waist circumference

1-OH-NAP: 1-hydroxynaphthalene

1-OH-PHE: 1-hydroxyphenanthrene

2-OH-DBF: 2-hydroxydibenzofuran

2-OH-FLU: 2-hydroxyfluorene

2-OH-NAP: 2-hydroxynaphthalene

3-OH-FLU: 3-hydroxyfluorene

## 6. TERMS

The author did not use specific or rare terms.

# 7. INTRODUCTION

Nodular goiter (NG) is the most common thyroid pathology in the general population, with an incidence of 5.0-10% worldwide [1,2]. NG is an enlarged thyroid gland with one or more areas of thyroid tissue that have undergone excessive growth, structural and/or functional transformation [1]. The prevalence of thyroid nodules varies depending on the investigated population and screening methods used for detection; 2-6% with palpation, 19-68% with ultrasound and 8-65% in autopsy [3,4].

NG can be uni-nodular, where the nodule is more than 5mm in diameter or multinodular (MNG); where 2 or more nodules exceed 5mm in diameter [5]. Majority are asymptomatic, especially if they are small in a euthyroid patient. However, local compressive symptoms can manifest if the goiter grows large enough to compress against surrounding structures in the neck [6,7].

The aetiology of NG is considered to be multifactorial with a combination of various environmental exposures, genetic predisposition, and endogenous factors that accelerate and influence the process of follicular cell hyperplasia [6,8]. Epidemiological studies have implicated non-modifiable factors such as genetics, age, gender and modifiable risk factors like iodine intake and goitrogens in the development of goiter and nodule formation [9]. Although these factors have been identified, the exact pathogenesis of NG is not completely elucidated.

The majority of studies on NG have been focused on specialised study populations such as the elderly, middle aged women or individuals with specific chronic diseases such as diabetes mellitus. Very few have been conducted in a population- based manner to focus on the incidence of NG [9]. Only in recent years, have large-scale population-based studies been performed so data on how the general population are affected by NG is lacking.

NG is also the most prevalent thyroid lesion encountered during surgical practice, due to its association with cancer development. Previous literature has noted that incidence of cancer is higher in single NGs than MNGs; with incidences of ~10-20% and ~5-10% respectively [2]. Early exclusion of malignancy is one of the goals in NG management. In previous years, a positive family history, history of irradiation, male gender, younger age, suspicious US findings, and symptoms of airway compression have been noted to increase malignancy risk in patients with NG [10,11].

Due to its high prevalence worldwide, and its potential significant clinical implications, it is necessary its relationship with risk factors, in order to aid its management and prevention. This systemic literature review was conducted in order to determine which factors were associated with NG in the general population and can be used as independent predictors of disease development. In addition to which factors present in NG patients can be used as indicators of malignancy.

# 8. AIM AND OBJECTIVES

**Aim:** To conduct a systematic review of factors associated with nodular goiter in the general population.

**Objectives**

- To determine the prevalence of nodular goiter amongst general populations.
- To determine the associations of modifiable and non-modifiable factors with nodular goiter.
- To determine which factors independently increase the risk of nodular goiter in different populations.
- To determine which factors play a role in the development of malignancy in individuals with nodular goiter.

# 9. LITERATURE REVIEW

Amongst thyroid diseases, nodular goiter is the most common pathology in the general population. Its incidence of 5.0 -10% increases with age and is more predominant in women [1,2]. The prevalence of thyroid nodules varies depending on the investigated population and screening methods used for detection; 2-6% with palpation (1% in men, 5% in women in iodine sufficient areas), 19-68% with ultrasound and 8-65% in autopsy [3,4]. An increasing prevalence has been noted in recent years due to the developments in imaging modalities used for diagnosis [12].

### 9.1 Classification:

Goiter is defined as a large thyroid volume that exceeds a total volume of 18ml in women and 25ml in men [1]. NG is as an enlarged thyroid gland with one or more areas of thyroid tissue that have undergone excessive growth, structural and/or functional transformation [1]. It can be uni-nodular where the nodule is more than 5mm in diameter or multinodular (MNG); where 2 or more nodules exceed 5mm in diameter [5]. Nodules can be normal, hyper- or hypo-functioning [13].

NG with single or multiple nodules can be classified as toxic or nontoxic. Toxic nodular goiter (TNG) is heterogeneous, where nodules on the enlarged thyroid are autonomously functioning, thereby producing excess thyroid hormone that results in suppressed TSH or symptoms of hyperthyroidism [1]. When the nodular enlargement is unrelated to overt hyper- or hypothyroidism, neoplastic or inflammatory processes, it is classified as ‘nontoxic’ or ‘euthyroid’ goiter (NNG). It is believed that NG is originally nontoxic, but with TSH dysregulation, some (~10%) nodules acquire functional autonomy, progressing into TNG [9].

### 9.2 Aetiology and pathogenesis

The exact aetiology of NG is not completely understood, varying from one patient to another. It is thought to be multifactorial with a combination of various environmental exposures, genetic predisposition, and endogenous factors acting to accelerate and influence the goitrogenic process [6,8]. Non-modifiable factors such as genetics, age, and gender have been implicated in the aetiology of goiter. Modifiable risk factors found to contribute to development include: iodine intake, goitrogens in food and water, body weight, nutrition status, smoking, drugs, infections and pollution [9].

All diffuse goiters have the capacity to transform into NGs with time. Initially diffuse hyperplasia of the gland results from either iodine deficiency or any of the factors mentioned above. The thyrocyte proliferation and $H_2O_2$ mediated DNA damage lead to an increased mutational load. These mutations in genes that code for TSH receptors or $G_s\alpha$ proteins initiate the cyclic AMP cascade responsible for growth and function of thyrocytes. In turn, a multitude of growth factors including IGF1 (insulin-like growth factor-1) and EGF (epidermal growth factor) are increasingly expressed, stimulating most cells to divide

and form small clones. The small clones containing mutations become self-stimulating and continue the cycle of uncontrolled proliferation, thus forming nodules [6,14,15].

Nodular goiter is a consequence of follicular cell hyperplasia in one or more areas of the thyroid. The follicular hyperplasia is primarily due to the heterogeneity of intrinsic growth potential in response to growth stimulating factors [6].

### 9.3 Clinical manifestations

The clinical manifestations of NG can vary and greatly depend on thyroid size, location and functional status. Majority are asymptomatic, especially if they are small in a euthyroid patient. In some cases, there may be complaints of a bulk or a tightening feeling in the neck [6,7,16]. Conversely, local compressive symptoms can manifest if the goiter grows large enough to compress against surrounding structures in the neck including the oesophagus, trachea and recurrent laryngeal nerve. Symptoms include dysphagia, hoarseness, dyspnoea, tracheal deviation, choking sensation, hyperthyroidism, cosmetic complaints and more rarely: recurrent or phrenic nerve palsy and Horner's syndrome. Presence of these symptoms indicates that the NNG is either retrosternal or migrated into the upper mediastinum [6,7].

Risk of developing these compressive symptoms or malignancy or toxicity make the assessment of uni- or multinodular goiter a necessity [9]. Nodular goiter can be detected by palpation, TSH measurement, ultrasonography (US), ultrasound-guided fine needle aspiration, during surgery and autopsy [1,2].

### 9.4 Iodine deficiency

Epidemiological studies have shown that goiter can be divided into endemic goiter where more than 10% of the population have goiter due to an iodine deficiency and sporadic goiter – less than 5% of iodine sufficient populations are affected [6,8]. These studies had found that most common factor causing endemic goiter was iodine deficiency caused by a low intake (<50 μg) in diet or water, that has been gradually eradicated via iodine prophylaxis programs [17,18].

Urinary iodine concentration (UIC) has been used as a biomarker of exposure to assess iodine status of populations. UIC measures the most recent intake of iodine (in μg/L), as >90% of iodine is excreted within 48hrs of ingestion. Majority of surveys are performed on children as they are a good general representation of the adult population [19]. The degree of iodine deficiency is classified based on the median 24-hour UIC: mild (60-120 μg), moderate (25-60 μg) and severe (<25 μg) [20].

Iodine fortification programs have been implemented worldwide, covering an estimated 71% of the total population [19]. They involve the introduction of iodised salt into the population's diet to reduce iodine deficiency. In a prospective, Danish population-based study investigating the effect of iodine

fortification programs on thyroid structure, it was found that the prevalence of goiter in all age groups had been reduced whereas that of nodules remained the same [21]. The Pescopagano study also concluded that goitre prevalence decreased with iodisation by the prevalence of NG in individuals under the age 35 [22].

Unlike diffuse goiter, in which its risk follows a U-shaped curve relationship with iodine intake; NG risk increases only with deficient iodine intake [19]. Yu et al. conducted a prospective 5-year, community-based study surveying 3 rural study populations living in areas of varying iodine levels. 1 cohort from an area of excess intake from iodised water (UIC 634 μg/L), another in a more than adequate intake of iodine (214 μg/L), and the third in mildly deficient area (88 μg/L). The respective cumulative incidences of NG were 0.8%, 2.4% and 5.0% [23].

### 9.5 Metabolic syndrome and nodular thyroid disease

Metabolic syndrome (MetS) is a cluster of conditions that has been found to increase the risk of chronic diseases such as cardiovascular disease by 2-fold and type 2 diabetes mellitus (T2DM) by 5-fold. It can therefore be used as a predictor of these diseases and other cardiometabolic disorders such as atherosclerotic cardiovascular disease (ASCVD) and stroke [24,25]. The increasing incidence of MetS worldwide has been linked to obesity, overnutrition, diabetes and physical inactivity, making it a global epidemic. It is estimated that MetS is present in every 1 in 4 of the adult population, with its prevalence increasing with age [24,26,27].

Although various definitions have been proposed, the common components agreed upon are: hypertension, increased fasting glucose (IFG), increased levels of triglycerides and decreased HDL in blood, and abdominal obesity that is determined either by waist circumference (WC) or BMI >30kg/$m^2$ [25,28].

In recent years, researchers have studied the link between MetS and thyroid nodular disease. Phitayakorn et al. conducted a study with 488 surgical patients with NG that identified obesity, older age and the African-American race as independent risk factors for large nodular goiters. BMI >30kg/$m^2$ was found to increase risk by 3-fold; a few theories were hypothesised to explain this finding. First that the increased neck and chest space found in individuals with a larger BMI conceals the growing NG until it is large enough to be recognised and compressive symptoms arise. The second being that the increased adipose tissue produces increased amounts of oestrogen, an endogenous hormone and known goitrogen that stimulates thyroid growth [25].

In a prospective case-control study, Ayturk et al. deduced that presence of insulin resistance in MetS patients led to a markedly increased thyroid volume and nodule incidence. Insulin resistance was established as an independent risk factor of nodule development via multivariate analysis [30].

### 9.6 Insulin resistance

Insulin resistance (IR) is a feature found in a multitude of disorders including T2DM, MetS, obesity, impaired glucose tolerance and polycystic ovarian syndrome (PCOS). IR is defined by a reduced sensitivity of peripheral tissues to insulin, that is compensated by increased insulin secretion to maintain metabolism. Preceding literature has linked IR to increased TV and nodule formation; concluding that increased circulating insulin results in higher TSH levels and unbound IGF-1 that effectuate increased thyrocyte proliferation and survival time via induction of antiapoptotic effects [24,29,31,32].

Metformin is a diabetic drug used to improve sensitivity to insulin. In recent years, the effect of metformin on thyroid volume and nodularity of both insulin resistant and non-resistant subjects has been studied. In IR individuals, metformin significantly reduced volume and nodule size. Similarly, one randomised study suggested that in subjects without IR, the drug seems to have a protective effect on nodule enlargement; it had significantly reduced endogenous TSH levels in euthyroid patients [33–35]. Although not completely elucidated, it is thought metformin acts by inhibiting IGF-1 and the AMPK/mTOR signalling pathways [36].

### 9.7 Lifestyle habits associated with nodular goiter

Smoking is a major global health issue, that has been implicated in the development of cardiovascular, respiratory and paraneoplastic diseases in addition to goiter. Cigarettes contain the goitrogenic compound thiocyanate: a competitive inhibitor of transport, active uptake and organification of iodine into thyroglobulin [6,29]. The relationship between smoking and the development of goiter has been studied in depth previously with various conclusions reached. The studied goiter was multinodular in the majority of articles. It has been suggested that its effect on NG is modified by iodine intake; it pronounces the effect of iodine deficiency on the thyroid, whilst the synergistic effect is not seen in iodine replete areas [1,37].

In a 5-year follow-up study conducted in an area of improved iodine supply by Itterman et al., smoking was only associated with thyroid growth in older individuals (> 60 years) with previous goiter diagnosis. No correlation was determined with younger individuals (aged <40 years), instead an inverse relationship was noted. The studied region was formerly iodine-deficient before the implementation of an iodisation program, leading to a conclusion that smoking exerted no effect on TV in areas of adequate iodine supply [38].

In 2002, Knudsen et al. reported a positive correlation between smoking (20g of tobacco per day minimum) and thyroid multi-nodularity (OR 1.9 (95% Cl: 1.4- 2.5), but one could not be found with solitary nodules. It was observed that heavy smokers were at twice the risk compared to non-smokers (16.5% vs 7.6%). With the association significantly augmented ($p$ =0.08) in areas of marked iodine-deficiency [39]. Galanti et al. [40] found in their cohort study of 874,507 parous women that smoking

increased the risk of nontoxic goiter and nodules in iodine deficient areas (endemic). The study being conducted on female subjects only limits the interpretation of smoking's effects on the general population.

In preceding studies, alcohol consumption has been associated with a lower occurrence of goiter. The psychoactive substance induces direct cellular toxicity on thyrocytes resulting in suppression and reduced volume of the gland [41]. Hegedüs et al. reported a lower prevalence of goitre in chronic alcoholic patients compared with control patients [42]. Knudsen et al. conducted a cross-sectional population study that concluded that moderate to high alcoholic intake correlated to a lower prevalence of both thyroid enlargement and nodules [43].

### 9.8 Nodular Goiter and Cancer

Previous studies have found that the occurrence of cancer has been higher in single NGs than MNGs; with incidences of ~10-20% and ~5-10% respectively [2]. Nodules are suspected of malignancy if the following criteria are found during US evaluation: solid structure, increased height/width ratio, increased central vascularity, have microcalcifications, are hypoechogenic, irregular/rough margins and halos that are either absent or thick and irregular [2,10].

Risk factors for MNG malignancy have been investigated in various literature. Rago et al. reported young age (OR 0.97), male gender (OR 1.44) and presence of solitary instead of multiple nodules (OR 0.63) as independent risk predictors ($p < 0.0001$) of papillary thyroid cancer (PTC) [44]. Both Rios et al. and Botrugno et al. conducted retrospective studies that aimed to identify clinical risk factors in MNG patients for malignancy. From the 672 MNG patients investigated by Rios et al., 59 cases presented with a thyroid carcinoma. Whereas Botrugno et al. found 41 incidental carcinoma cases from their 462-study population. In both studies, PTC was the most common histological type. Both authors determined a family history of thyroid disease and a personal history of cervical radiation therapy as clinical risk factors for malignancy. Rios et al. also reported presence of recurrent goiter or cervical adenopathies are independent variables, whilst Botrugno et al. stated US detection of calcifications [45,46].

# 10. MATERIALS & METHODS

## 10.1 Protocol

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed to carry out this review. The analysis, inclusion and exclusion criteria were defined beforehand. The focus of this systematic review is outlined in the objectives.

## 10.2 Types of studies

The review included retrospective and prospective articles published between 2011 and 2021 that were written in English.

## 10.3 Information sources

The information sources used were PubMed, Science Direct, Scopus, Springer Link, Karger open access, the Cochrane Central Register of Controlled Trials (CENTRAL), and Wiley Online Library.

## 10.4 Type of population

The studies included patients of both sexes aged above 18 years old who were diagnosed with nodular goiter (single or multinodular), enlarged thyroid volume/goiter or thyroid nodules.

## 10.5 Literature search strategy

The information sources listed in 10.3 were electronically searched for studies. Within the listed databases, the following search terms were used to identify relevant papers: ‘Nodular goiter’, ‘factors contributing to nodular goiter’, ‘nodular goiter factors’, and ‘goiter with nodules’, ‘Nodular goiter population study’ and ‘nodular thyroid disease’. In addition, phrases that combined ‘nodular goiter’ with ‘aetiology’, ‘incidence’, ‘risk factors’, ‘causes’, ‘cancer’ and ‘malignancy risk factors’ were also used. In CENTRAL, Wiley Online Library and Science Direct, this search was conducted separately under the filters of: ‘Title, Abstract or Keywords’.

The abstracts of all potential papers were screened for relevance in the above-mentioned databases during the first stage search.

## 10.6 Inclusion and Exclusion Criteria

**Table 1. The inclusion and exclusion criteria used to select studies for this review.**

| Inclusion criteria: | Exclusion criteria: |
|---|---|
| Studies of patients that present with NG/ thyroid nodules/ goiter | Studies where full-text is not available |
| Studies focused on the influence of factors on NG incidence | Systemic reviews, literature reviews, metanalysis papers |
| Studies written in the English language | Studies published before 2011 |
| Studies on humans | Studies written in a language other than English |
| Studies published from 2011 to 2021 | Studies on animals |
| Sufficient data to correspond to a 95% confidence interval | Similar studies conducted by the same authors |

## 10.7 Sequential search strategy

During the second stage search, full text versions of the papers selected for screening were assessed for eligibility using the inclusion and exclusion criteria listed in table 1. To avoid omission, the articles gathered were then further searched for referenced publications to identify any additional papers relevant to this review. The search was limited to the English language. A flow diagram of study selection according to PRISMA 2020 guidelines was prepared (figure 1).

## 10.8 Data extraction

Each full article was read and the following data was independently extracted according to the present review's aims and objectives:

- "Author" - The author of the publication
- "Year" - The year of the publication
- "Country" - The country in which the study was performed
- "Type of study" – The type of study
- "Aim of study" - The purpose of each study
- "Sample size" - The number of eligible patients included
- "Age" - The age of participants in the study
- "Inclusion criteria" - The inclusion criteria in the study
- "Exclusion criteria" - The exclusion criteria in the study
- 'Independent risk factor', 'independent predictor' & "significant association of factors"
- "Odds ratio", "p value", "r value"
- Conclusions

## 10.9 Statistical analysis

No meta-analysis was performed

## 10.10 Selection of articles

The PRISMA 2020 flow diagram was used to record the number of studies found during the electronic search, the papers that were included and excluded with reasons and the number of studies selected for the systematic review. Overall, 27 articles were assessed as eligible and included in this review: 8 were from China, 5 from Turkey, 3 from Italy, and 1 from Greece, Ireland, Taiwan, Peru, Korea, Jordan, Serbia, USA and Israel respectively.

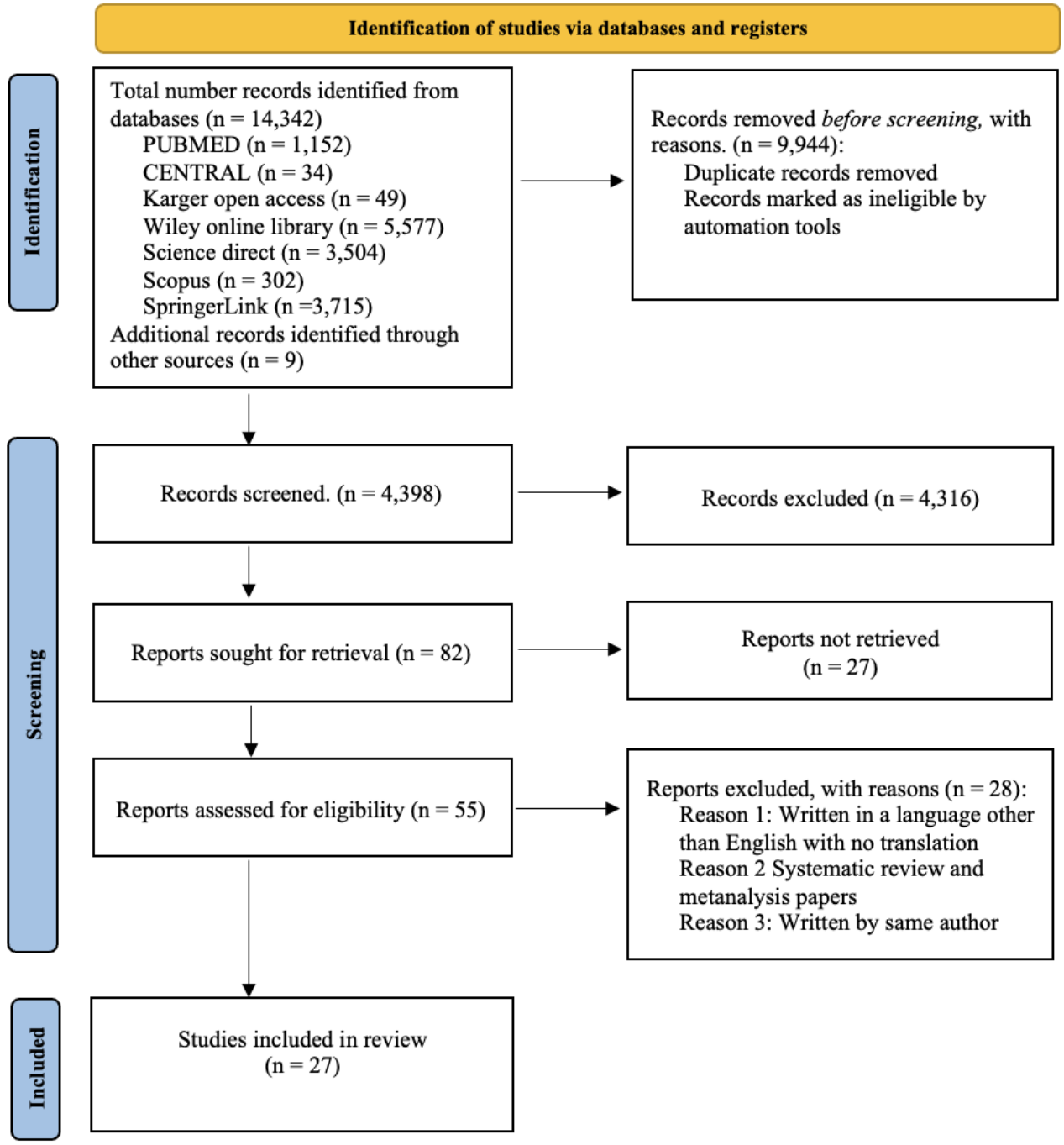



Figure 1: Prisma flowchart

# 11. RESULTS

## 11.1 Factors associated with nodular goiter

**Table 2. Characteristics of included studies**

| No | Author, year | Country | Study Type | Sample size | [a] Mean age | Aim of study |
|---|---|---|---|---|---|---|
| **1** | Aydin et al. 2011 [47] | Turkey | Prospective | 2,298 | 50 | To determine the association between smoking habit, goiter, thyroid functions and US nodularity in moderately iodine deficient area. |
| **2** | Rendina et al. 2012 [28] | Italy | Retrospective | 2,632 | 64.2 ±17.8 | To evaluate the relationship between MetS and multinodular non- toxic goiter in an inpatient population from a geographic area with moderate iodine deficiency |
| **3** | Anil et al. 2013 [48] | Turkey | Prospective | 279 | 53.25 + 7.13 | To evaluate TV and nodule prevalence in patients with pre-diabetes and T2DM in a mild-to-moderate iodine deficient area. |
| **4** | Ovadia et al. 2014 [5] | Israel | Prospective | 62 | 57 ± 13 | To estimate iodine intake and explore its correlation with thyroid diseases among Israeli adults living near the Mediterranean coast. |
| **5** | Rendina et al. 2015 [49] | Italy | Retrospective | 1800 | 64.0 ±16 | To evaluate the relationship between tobacco smoking, smoking cessation, and the prevalence of SNG and HT in patients consecutively referred to the Spinelli Hospital, in a time span of 2 years. |
| **6** | Feng et al. 2016 [50] | China | Retrospective | 6494 | 55.3 ± 0.37 | To investigate the prevalence of TNs and their association with MetS in a moderate iodine intake area of Jiangsu, China. |
| **7** | Jiang et al. 2016 [51] | China | Retrospective | 6,324 | 52.15 ±11.58 | To determine the prevalence of TNs, their epidemiological characteristics, and their correlation with lifestyle factors. |
| **8** | Buscemi et al. 2017 [52] | Italy | Prospective | 1,201 | 50.35 ± 9.07 | To investigate the association between TN, obesity, diabetes, and dietary habits. |
| **9** | Dauksiene et al. 2017 [53] | Lithuania | Prospective | 317 | 48-49 (48.5) | To determine associations of thyroid hormone levels and different metabolic parameters and anthropometric measurements with volume of nodular and nonnodular thyroid as well as with prevalence of goiter and thyroid nodules in middle-aged euthyroid subjects. |
| **10** | Karaköse et al. 2017 [54] | Turkey | Retrospective | 168 | 24.2 ± 5.37 | To detect the prevalence of AITD and NG in patients with PCOS and investigate whether PCOS-related hormones and metabolic factors affect them. |
| **11** | Zhou et al. 2017 [55] | China | Retrospective | 178 | N/A | To investigate if an association exists between BPA levels and excessive iodine intake and NG and PTC |
| **12** | Aydoğan et al. 2018 [56] | Turkey | Retrospective | 100 | 39.5 | To reveal whether or not IR, nodule presence, and nodule stiffness affect arterial stiffness in individuals with euthyroid nodular goiter using PWA. |
| **13** | Fan et al. 2018 [57] | China | Retrospective | 2,647 | 58.14 ± 8.9 | To identify possible factors that may influence TN prevalence through thyroid US, questionnaires, and physical examination. |

| | | | | | | |
|---|---|---|---|---|---|---|
| **14** | Kir et al. 2018 [58] | Turkey | Prospective | 1,432 | 50 ± 15 | To evaluate potential factors associated with thyroid nodularity. Part of prospective Melen study. |
| **15** | Moon et al. 2018 [59] | Korea | Retrospective | 63,259 | 49.58 ± 10.35 | To investigate the prevalence and characteristics of TNs and their associated clinical parameters in the healthy Korean population at health check-ups. |
| **16** | Song et al. 2018 [60] | China | Retrospective | 1,482 | 44.5 ± 15.4 | To examine whether TNs are associated with overweight and obesity, as defined with BMI and waist circumference. |
| **17** | Guo et al. 2019 [61] | China | Retrospective | 2606 | 43.08 ± 15.51 | To evaluate the relationships between MetS and TN and TV in an adult population. |
| **18** | Su et al. 2019 [62] | China | Retrospective | 927 | 53.4 | To investigate the relationship between TN and TV and MetS and its components in an iodine-adequate area in Asia. |
| **19** | Mayers et al. 2019 [63] | Peru | Retrospective | 182 | 50.5 | To determine the association between MetS and nodular thyroid disease in a region with adequate iodine intake. |
| **20** | Tseng et al. 2019 [64] | Taiwan | Prospective | 40,096 | 68.72 ± 12.73 | To investigate whether metformin might affect the risk of benign nodular goiter in patients T2DM. |
| **21** | Chen et al. 2021 [65] | China | Retrospective | 1,279 | 44.97 ± 14.47 | To investigate the effects of obesity, smoking and drinking on the prevalence of SHO and TNs. |
| **22** | Liu et al. 2021 [66] | China | Retrospective | 201 | 53.03 ± 11.56 | To investigate the relationship between urinary metabolites of PAH and risk of PTC and NG in non-occupational populations. |

[a] Mean age (±SD)

AITD: autoimmune thyroid disease, BMI: Body mass index, BPA: bisphenol A, HT: Hashimoto's thyroiditis, IR: Insulin resistance, MetS: Metabolic Syndrome, NG: Nodular goiter, PAH: Polycyclic aromatic hydrocarbons, PCOS: Polycystic ovary syndrome, PTC: papillary thyroid carcinoma, PWA: pulse wave analysis, SHO: subclinical hypothyroidism, SNG: Simple nodular goiter, TN: Thyroid Nodules, TV: Thyroid Volume, T2DM: Type 2 diabetes mellitus, US: Ultrasonography

**Table 3: Prevalence of Thyroid Nodules in each study population in included studies**

| | | | Total study population | | | | TN population | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Author | Country | Number of subjects | Males (%) | Females (%) | Mean age of all subjects (years) | TN Prevalence (%) | Male with TN (%) | Females with TN (%) | Mean age of TN subjects (years) |
| **1** | Anil et al. 2013 [48] | Turkey | 393 | 125 (31.8) | 268 (68.2) | 53.25 + 7.13 | 183 (46.6) | 125 (31.8) | 268 (68.2) | N/A |
| **2** | Feng et al. 2016 [50] | China | 6494 | 2427 (37.4) | 4067 (62.6) | 55.3 ± 0.37 | 1150 (17.7) | 312 (27.1 | 838 (72.8) | 56.24 ± 0.50 |
| **3** | Jiang et al. 2016 [51] | China | 6,324 | 2264 (35.8) | 4060 (64.2) | 52.15 ±11.58 | 3,100 (49) | 967 (42.7) | 2133 (52.5) | N/A |
| **4** | Buscemi et al. 2017 [52] | Italy | 1,201 | 455 (37.9) | 746 (62.1) | 50.35 + 9.07 | 475 (39.5) | 160 (33.7) | 315 (66.3) | 54 ± 11 |
| **5** | Dauksiene et al. 2017 [53] | Lithuania | 317 | 142 (44.8) | 175 (55.2) | 48.5 | 99 (31.2) | 28 (28.3) | 71 (71.7) | 48.5 |
| **6** | Fan et al. 2018 [57] | China | 2,647 | 1,352 (51.1) | 1,295 (48.9) | 43 ± 15.49 | 698 (26.3) | 320 (23.4) | 378 (29.1) | N/A |
| **7** | Moon et al. 2018 [59] | Korea | 63,259 | 32,541 (51.4) | 30,718 (48.6) | 49.58 ± 10.35 | 24,686 (34.13) | 9,900 (40.1) | 14,786 (59.9) | 52.7 ±10.4 |
| **8** | Guo et al. 2019 [61] | China | 2606 | 1338 (51.34) | 1268 (48.66) | 43.08 ± 15.51 | 681 (26.1) | 315 (46.36) | 366 (53.74) | 50.14 ± 14.92 |
| **9** | Song et al. 2018 [60] | China | 1482 | 682 (46.0) | 800 (54.0) | 44.5 ±15.4 | 187 (12.6) | 77 (41.2) | 110 (58.8) | 54.6 ± 15.3 |
| **10** | Su et al. 2019 [62] | China | 927 | 365 (39.4) | 562 (60.6) | 53.4 | 269 (29) | N/A | N/A | N/A |
| **11** | Chen et al. 2021 [65] | China | 1,279 | 524 (41.0) | 755 (59.0) | 44.97 ± 14.47 | 238 (18.6) | 78 (14.9 %) | 160 (21.2 %) | 52.84 ± 14.65 |

Mean age (± SD)

TN: Thyroid nodule

## Table 4: Independent risk factors associated with Thyroid Nodules

| | Author | Age | Female sex | TSH | TV/ Goiter | BMI | MetS | Fasting glucose (FPG) | HDL | WC | Hypertension | DM | Thyrotox-icosis | Smoking | Alcohol | Milk consumption | Higher educational level | Physical labour |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Anil et al. 2013 [48] | $p=0.045$ OR 1.03 (1.00–1.06) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | $p<0.0001$ OR 4.55 (2.48–8.34) | N/A | N/A | N/A | N/A | N/A | N/A |
| 2 | Feng et al. 2016 [50] | p <0.001 OR 1.040 (1.034–1.045) | p <0.001 OR 2.012 (1.695–2.389) | N/A | N/A | N/A | N/A | p <0.001 OR 1.357 (1.152–1.600) | N/A | p =0.002 OR 1.264 (1.091–1.466) | p <0.001 OR 1.516 (1.141– 1.546) | N/A | N/A | p =0.003 OR 1.309 (1.099–1.558) | N/A | N/A | N/A | N/A |
| 3 | Jiang et al. 2016 [51] | $p<0.001$ OR 1.039 (1.034–1.044) | $p<0.001$ OR 1.789 (1.527–2.097) | N/A | N/A | $p=0.006$ OR 1.019 (1.005–1.034) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | $p=0.014$ OR 1.246 (1.046–1.483) | N/A | N/A | N/A | N/A |
| 4 | Buscemi et al. 2017 [52] | $p<0.001$ | $p<0.001$ | N/A | N/A | $p<0.001$ | N/A | N/A | N/A | N/A | N/A | $p<0.001$ | N/A | N/A | N/A | $p=0.048$ | N/A | N/A |
| 5 | Dauksiene et al. 2017 [53] | N/A | $p<0.001$ OR 4.29 (1.98–9.31) | $p=0.028$ OR 1.61 (1.05–2.45) | $p<0.001$ OR 1.16 (1.09–1.23) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| 6 | Fan et al. 2018 [57] | $p<0.001$ [a] OR 3.221 (2.255–4.603) [b] OR 4.371 (2.974–6.425) [c] OR 6.694 (4.545–9.858) | $p<0.001$ OR 1.600 (1.239–2.067) | N/A | $p<0.001$ OR 4.341 (2.064–9132) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | $p<0.006$ OR 1.871 (1.201–2.912) | $p<0.014$ OR 1.553 (1.093–2.206) |
| 7 | Moon et al. 2018 [59] | $p<0.001$ OR 1.045 (1.045-1.049) | $p<0.001$ OR 2.295 (2.213-2.380) | N/A | N/A | $p<0.001$ OR 1.033 (1.026-1.041) | $p<0.001$ OR 1.086 (1.013–1.165) | N/A | N/A | N/A | N/A | N/A | $p<0.001$ OR 1.629 (1.464–1.814) | N/A | N/A | N/A | N/A | N/A |
| 8 | Song et al. 2018 [60] | N/A | N/A | N/A | N/A | $p=0.044$ [d] OR 1.61, (1.01–2.54) [e] OR 1.95, (1.14–3.34) [f] OR 5.15, (1.30–20.37) | N/A | N/A | N/A | $p=0.044$ [g] OR 1.87, (1.05–3.32) $p=0.048$ [h] OR 1.54, (1.00–2.37) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| 9 | [i] Guo et al 2019 [61] | N/A | N/A | N/A | N/A | N/A | p =0.0429 OR 1.23 (1.00–1.51) | N/A | N/A | N/A | p =0.0130 OR 1.29 (1.06–1.58) | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| 10 | Su et al. 2019 [62] | $p<0.001$ OR 1.05 (1.037- 1.065) | N/A | N/A | N/A | N/A | N/A | N/A | $p=0.0023$ OR 0.45 (0.27- 0.75) | $p=0.0036$ OR 1.04 (1.02-1.06) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| 11 | Chen et al. 2021 [65] | N/A | N/A | N/A | N/A | $p=0.015$ [j] OR 2.069 (1.149–3.724) $p=0.005$ [k] OR = 3.065, (1.413–6.648) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | $p=0.01$ [l] OR 0.456, (0.240–0.865) $p=0.029$ [m] OR 0.467, (0.236–0.925) | N/A | N/A | N/A |

*p* value is given first, followed by Odds ratio (95% Confidence Level) – OR (95% Cl). Only significant associations are presented.

BMI: Body mass index, DM: Diabetes mellitus, HDL: High density lipoprotein, MetS: Metabolic syndrome, N/A: Not available, TSH: Thyroid-stimulating hormone, TV: Thyroid volume, WC: Waist circumference

[a] OR value for age ~40.

[b] OR value for age ~50.

[c] OR value for age ~60.

[d] BMI $\geq$45kg/m$^2$ in women. OR adjusted for age, education, profession, smoking status, systolic and diastolic blood pressure, TSH, and UIC.

[e] BMI $\geq$25kg/m$^2$ in women. OR adjusted for age, education, profession, smoking status, systolic and diastolic blood pressure, TSH, and UIC.

[f] BMI $\geq$25kg/m$^2$ in individuals with TSH >4.2 mIU/L. OR adjusted for age, gender, education, profession, smoking status, systolic and diastolic blood pressure, and UIC.

[g] OR value for individuals with central obesity aged < 50 years old.

[h] OR value for individuals with central obesity aged > 50 years old.

[i] OR adjusted for age, gender, education, income, smoking status, and salt intake.

[j] BMI $\geq$25kg/m$^2$ in people over 60 yrs. OR adjusted for gender, drinker, smoker.

[k] BMI $\geq$25kg/m$^2$ in drinkers. OR adjusted for gender, age, BMI, smoker.

[l] Alcohol in smokers. OR adjusted for gender, age, drinker, BMI.

[m] Alcohol in people with BMI $\geq$25kg/m$^2$. OR adjusted for gender, drinker, smoker.

**Table 5: Prevalence of Thyroid Volume in each study population in included studies**

| | Author | Country | Total study population: Number of subjects | Males (%) | Females (%) | Mean age of all subjects (years) | TV population: TV Prevalence (%) | Male with TV (%) | Females with TV (%) | Mean TV (mL) |
|---|---|---|---|---|---|---|---|---|---|---|
| **1** | Aydin et al. 2011 [47] | Turkey | 2,298 | 827 (36) | 1471 (64) | 50 | N/A | N/A | N/A | 18.67 ± 15.32 |
| **2** | Anil et al. 2013 [48] | Turkey | 393 | 125 (31.8) | 268 (68.2) | 53.25 + 7.13 | N/A | N/A | N/A | 16.79 ± 7.32 |
| **3** | [1]Dauksiene et al. 2017 [53] | Lithuania | 317 | 142 (44.8) | 175 (55.2) | 48.5 | 39 (12.3) | 12 (30.8) | 27(69.2) | 16.5 ± 6.0<br>12.3 ± 5.0 |
| **4** | Guo et al. 2019 [61] | China | 2,606 | 1,338 (51.34) | 1,268 (48.66) | 43.08 ± 15.51 | N/A | N/A | N/A | 9.97 ± 4.70 |
| **5** | [1]Su et al. 2019 [62] | China | 927 | 365 (39.4) | 526 (60.6) | 53.4 | N/A | N/A | N/A | 14.96<br>13.26 |

[1]Mean TV: male TV given first, then female TV. TV: Thyroid Volume

**Table 6: Independent risk factors associated with Thyroid Volume/ Goiter**

| | Author | Age | Female sex | Nodules | TSH | BMI | Elevated BP | MetS | WC | Abdominal adiposity | TG | T2DM | Smoking |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | Aydin et al. 2011 [47] | *p* <0.001 OR: 1.039 (1.031 - 1.047) | *p* <0.001 OR: 2.579 (1.900 - 3.501) | N/A | *p* <0.001 OR: 1.828 (1.423 - 2.347) | *p* <0.001 OR: 1.030 (1.013- 1.048) | N/A | N/A | N/A | N/A | N/A | N/A | *p* =0.034 OR: 1.459 (1.029 - 2.068) |
| **2** | Anil et al. 2013 [48] | p =0.004 | N/A | N/A | N/A | N/A | N/A | N/A | p <0.0001 | N/A | N/A | p <0.0001 | N/A |
| **3** | Dauksiene et al. 2017 [53] | N/A | *p* =0.009 OR 4.46 (1.46–13.61) | *p* =0.001 OR 4.13 (1.82–9.38) | *p* <0.001 OR 0.09 (0.03–0.26) | *p* =0.001 OR 1.26 (1.1–1.44) | N/A | N/A | N/A | N/A | N/A | N/A | *p* = 0.002 OR 3.91 (1.68–9.06) |
| **4** | Guo et al. 2019 [61] | N/A | p < 0.0001 | p < 0.0001 | N/A | p <0.0001 | p <0.0001 | p =0.0037 | N/A | p =0.0162 | p =0.0369 | N/A | N/A |
| **5** | Su et al. 2019 [62] | N/A | N/A | N/A | N/A | N/A | N/A | N/A | p =0.02 | N/A | N/A | N/A | N/A |

*p* value is given first, followed by Odds ratio (95% Confidence Level) – OR (95% Cl). Only significant associations are presented.

BMI: Body mass index, TN: Thyroid nodules, TSH: Thyroid-stimulating hormone, TG: Triglycerides, T2DM: Type 2 Diabetes mellitus, WC: Waist circumference

A total of 86,929 individuals were eligible to be included in the studies to evaluate which factors increased risk of TN formation. All studies presented the gender distribution of the study population included. From the data provided, 44,714 women and 42,215 men were included. The mean age of all patients in the chosen studies was 48.92 years old [48,50–53,57,59–62,65].

Of the 86,929 individuals, 31,766 people had TNs (~36.5%). Table 3 demonstrates the demographic characteristics of each study population in the chosen articles investigating TNs. All excluding Su et al. [62] demonstrated a predominance of women. Su et al. is the only study to not include the distribution of males and females with nodules [48,50–53,57,59,60,65,67]. From the data given, the mean age of subjects with TNs was older than that of the total study population [52,53,59–61,65].

Based on the articles, the most common factors independently associated with increased risk of thyroid nodules are age ($p < 0.001$), female sex ($p < 0.001$) and BMI ($p < 0.05$). Fan et al. stratified age into decade groups and reported risk significantly increased with each decade ($p<0.001$) [47,50–53,57,59,60,65].

Feng et al. conducted a community-based study focusing on the association of components of MetS with TNs prevalence. Multivariate logistic regression analysis demonstrated significant associations with increased age (OR 1.040 (95% Cl: 1.034- 1.045), $p < 0.001$), female gender (OR 2.012 (95% Cl: 1.695- 2.389), $p < 0.001$) and smoking (OR 1.309 (95% CI 1.099–1.558), $p = 0.003$). Components of MetS that were significantly associated TN incidence included: elevated WC (OR 1.264 (95% CI: 1.091–1.466), $p = 0.002$), increased FPG (OR 1.357 (95% CI: 1.152–1.600), $p < 0.001$), and hypertension (OR 1.328 (95% CI 1.141–1.546), $P < 0.001$) [44].

Jiang et al. carried out a large-scale cross-sectional study on how the incidence of TNs correlated to the presence of epidemiological and lifestyle factors. The results were that age (OR 1.039 (95% Cl: 1.034–1.044), $p < 0.001$), female gender (OR 1.789 (95% Cl: 1.527–2.097), $p < 0.001$), BMI (OR 1.019 (95% Cl: 1.005–1.034), $p = 0.006$), and current smoking habits (OR = 1.246 (95% Cl: 1.046–1.483), $p = 0.017$) were independently increased risk of TN development [51].

Buscemi et al. assessed the relationship between thyroid nodules presence and obesity, DM and dietary habits. Pearson correlation coefficient calculations showed a positive correlation between the number of thyroid nodules and age ($r = 0.19$; $P < 0.001$), gender ($r = 0.08$; $P = 0.005$) and BMI ($r = 0.07$; $P = 0.02$) respectively. Whilst multivariate analysis results suggested independent correlations between age, gender, BMI ($p < 0.001$), diabetes mellitus ($p = 0.001$) and habitual consumption of milk ($p = 0.048$ with thyroid nodule presence [52].

Chen et al. examined the correlation between TNs and lifestyle risk factors: BMI, smoking habits and alcohol consumption. Analysis demonstrated that BMI $\geq$ 25 kg/m$^2$ and drinking were both independently associated with a significant increase in TNs risk. A significant association was found between TNs incidence and BMI $\geq$ 25 kg/m2 in adults above the age of 60 (OR 2.069 (95 % CI: 1.149–

3.724), $p$ =0.015) and drinkers (OR 3.065 (95 % CI: 1.413–6.648), $p$ =0.005). Alcohol consumption exerted a protective effect on nodule formation in both smokers (OR 0.456 (95 % CI: 0.240–0.865), $p$ = 0.016) and individuals with BMI ≥ 25 kg/m$^2$ (OR 0.467 (95 % CI: 0.236–0.925, $p$ = 0.029) [65].

Fan et al. conducted a study that focused on factors that significantly influenced the increasing prevalence of TNs in Tianjin, China. Their analysis revealed that independent risk factors for nodule prevalence were female gender (OR 1.600 (95% Cl: 1.239–2.067), p <0.001), goiter (OR 1.600 (95% Cl: 1.239–2.067), p <0.001), higher education (OR 1.871 (95% Cl: 1.201–2.912), $p$ <0.006*)*, physical labour (OR 1.553 (95% Cl: 1.093–2.206), $p$ <0.014*)* and older age (p <0.001). They found that risk significantly increased from the age of 40 years with each decade (OR 3.221 (95% Cl: 2.255–4.603), OR 4.371 (95% Cl: 2.974–6.425), OR 6.694 (95% Cl: 4.545–9.858)) [57].

Moon et al. investigated the relationship between TNs and their related clinical parameters. Multivariate logistic regression analysis determined the factors that independently increased risk of TNs significantly (p<0.001). The independent risk factors were: age (OR 1.045 (95%CI: 1.045-1.049), female sex (OR 2.295 (95% Cl: 2.213-2.380), BMI OR 1.033 (95% Cl: 1.026-1.041), MetS (OR 1.086 (95% Cl: 1.013–1.165) and thyrotoxicosis OR 1.629 (95% Cl: 1.464–1.814) [59].

Song et al. explored the correlation between adiposity (BMI and central obesity) and presence of TNs. Central obesity was stated as a WC that exceeds 90cm in men and 80 cm in women. They found that BM1 ≥24 kg/m$^2$ (OR 1.61 (95% CI: 1.01–2.54), p =0.044), and BMI ≥25 kg/m$^2$ (OR 1.95 (95%CI: 1.14–3.34), p =0.044), significantly increased risk of TNs in females. An association between TNs and obesity was also found in subjects with TSH levels >4.2 mIU/L (OR 5.15, (95% Cl: 1.30–20.37), p= 0.044). Furthermore, central obesity was significantly associated with increased TN risk both subjects younger and older than 50 years (OR 1.87 (95%CI: 1.05–3.32) and OR 1.54 (95%CI: 1.00–2.37), which led to the conclusion that WC affects risk irrespective of age, and could be a better indicator of risk [60].

Aydin et al. performed a prospective study to establish if an association existed between smoking, thyroid volume, goiter and thyroid function. Multivariate regression analysis showed that heavy smoking, >20 packs/ year, was an independent risk factor of goiter formation (OR: 1.459 (95% Cl: 1.029 - 2.068), p =0.034). Analysis showed that age, female gender, abnormal TSH levels and BMI were also independent predictors (p<0.001) [47].

4 of the chosen articles focused on the prevalence of both TNs and TV and their respective associations with risk factors. Their findings are mentioned below.

Anil et al. examined the incidence of both TNs and TVs in diabetic patients living in an iodine-deficient part of Turkey. Multivariate analysis determined age (OR 1.03 (95% Cl: 1.00–1.06), p=0.045) and T2DM (OR 4.55 (95% Cl: 2.48–8.34), p < 0.0001) as independent risk factors of TN development.

The prospective, case-control study also used multiple linear regression which demonstrated that age, WC and T2DM were all independent predictors of TV ($p = 0.004$, $p < 0.0001$ and $p < 0.0001$ respectively)[48].

Dauksiene et al. focused on both the prevalence of thyroid nodules and goiter, as well as their association with thyroid hormones, metabolic and anthropometric values. The prospective study revealed that increased thyroid nodule prevalence is significantly associated with female sex, TV and higher TSH levels (OR 4.29 (95% Cl:1.98–9.31), $p < 0.001$; OR 1.16 (1.09–1.23), $p < 0.001$; OR 1.61 (95% Cl: 1.05–2.45), $p = 0.028$) respectively on multivariate analysis. In addition, analysis determined independent risk factors of goiter are TNs, low TSH levels, female sex, BMI and smoking (OR 4.13 (95% Cl: 1.82–9.38), $p = 0.001$; OR 0.09 (95% Cl: 0.03–0.26), $p < 0.001$; OR 4.46 (95% Cl: 1.46–13.61), $p = 0.009$; OR 1.26 (95% Cl: 1.1–1.44), $p = 0.001$; OR 3.91 (95% Cl: 1.68–9.06), $p = 0.002$) [53].

Guo et al. studied the association between TN and TV incidence and the presence of metabolic parameters. A multivariate binary logistic regression model that adjusted for confounding factors showed that both MetS and elevated blood pressure independently increased risk of TNs significantly (OR 1.23 (95% CI: 1.00–1.51), p =0.0429 and OR 1.29 (95% CI: 1.06–1.58), p = 0.0130 respectively). In regards to TV prevalence, results deduced that TNs, gender, BMI and elevated blood pressure ($p < 0.0001$), MetS (p =0.0037) abdominal adiposity (p =0.0162) and hypertriglyceridemia (p = 0.0369) were all independently associated with its increased risk [61].

Su et al. carried out a large community-based population study to understand how TV and TNs are related to components of MetS. MetS was associated with both TN and TV. Findings were assessed on a multivariate basis that concluded WC was an independent predictive factor for both thyroid nodules and volume (OR 1.04 (95% Cl: 1.02-1.06), $p<0.0036$ and $p=0.02$ respectively) whereas HDL was a protective factor (OR 0.45 (95% Cl: 0.27- 0.75), p =0.023) [62].

**Table 7: Demographics of Nodular Goiter cases in chosen studies**

| | | | Total study population | | | | NG population | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Author | Country | Number of subjects | Males (%) | Females (%) | Mean age of all subjects (years) | NG Prevalence (%) | Male with NG (%) | Females with NG (%) | Mean age of NG subjects (years) |
| **1** | Ovadia et al. 2014 [5] | Israel | 62 | 12 (19.4) | 50 (80.6) | 57 ± 13 | 17 (27.4) | 4 (23.5) | 13 (76.5) | 60 ± 10 |
| **2** | Rendina et al. 2015 [49] | Italy | 1800 | 723 (40.2) | 1077 (59.8) | 64.0 ±16 | 538 (29.9) | 176 (32.7) | 362 (67.3) | 67.4 ± 1.9 |
| **3** | Karaköse et al. 2017 [54] | Turkey | 168 | 0 (0) | 168 (100.0) | 24.2 | 40 (23.8) | 0 (0) | 40 (100) | N/A |
| **4** | Zhou et al. 2017 [55] | China | 178 | 50 (28.1) | 128 (71.9) | N/A | 60 (33.7) | 14 (23.3) | 46 (76.7) | N/A |
| **5** | Aydoğan et al 2018 [56] | Turkey | 100 | 21 (21.0) | 79 (79.0) | 39.5 | 50 (50) | 8 (16.0) | 42 (84.0) | 41 |
| **6** | Kir et al. 2018 [58] | Turkey | 1432 | 542 (37.8) | 890 (62.2) | 50 ±15 | 245 (17.1) | N/A | N/A | N/A |
| **7** | Mayers et al. 2019 [63] | Peru | 182 | 24 (15.2) | 158 (86.8) | 50 | 91 (50) | 8 (8.79) | 83 (91.2) | 50 |
| **8** | Tseng et al. 2019 [64] | Taiwan | 40,096 | 22,682 (56.6) | 17,414 (43.4) | 68.72 ± 12.73 | 613 (1.53) | N/A | N/A | N/A |
| **9** | Liu et al. 2021 [66] | China | 201 | 47 (23.4) | 154 (76.6) | 53.03 ± 11.56 | 104 (13.43) | 27 (26.0) | 77 (74.0) | 56.13 ± 11.38 |

Mean age is expressed as mean ± standard deviation

NG: Nodular goiter

## Table 8: Risk factors associated with Nodular Goiter

| | Author | | Older age | Female gender | BMI | MetS | Low HDL | Fasting Glucose (FPG) | Fasting / Insulin resistance | PWV | Serum TG | UBC | Iodine intake | Smoking | Parity | Alcohol | OH-PAHs | Metformin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | Ovadia et al. 2014 [5] | NG | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | *p* <0.05 | N/A | *p* <0.05 | N/A | N/A | N/A | N/A | N/A |
| ***2*** | Rendina et al. 2015 [49] | NG | OR 1.05 (1.02-1.09) | OR 1.91 (1.51-2.30) | OR 1.51 (1.21-1.87) | OR 1.34 (1.11–1.67) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | *p* <0.01 [c] OR 1.65 (1.28- 2.12) | N/A | OR 0.78 (0.70-0.85) | N/A | N/A |
| **3** | Karaköse et al. 2017 [h] [54] | TN | *p* =0.001 | N/A | *p* <0.001 | N/A | N/A | *p* =0.005 | *p* =0.004 | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| | | TV | *p* =0.026 r =0.172 | N/A | *p* <0.001 r = 0.330 | N/A | N/A | *p* =0.012 r =0.195 | *p* =0.006 r =0.212 | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| **4** | Zhou et al. 2017 [55] | NG | *p*=0.00 OR 1.12 (1.08-1.17) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | *p*=0.00 OR 6.15 (2.16-17.53) | *p*=0.03 OR 4.93 (1.17–12.10) | N/A | N/A | N/A | N/A | N/A |
| **5** | Aydoğan et al. 2018 [56] | NG | N/A | N/A | N/A | N/A | N/A | *p* = 0.03 | N/A | *p* <0.001 | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| **6** | Kir et al. 2018 [58] | NG | *p* <0.001 OR 1.03 (1.01-1.05) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| **7** | Mayers et al. 2019 [a][63] | NG | N/A | N/A | N/A | *p* <0.05 OR 2.96 (1.47 -5.95) | *p* <0.05 OR 2.77 (1.44 -5.3) | *p* <0.05 OR 2.23 (1.14 -4.34) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| **8** | Tseng et al. 2019 [64] | NG | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | [d] 0.527 (0.45 -0.62) *p* =0.09 [e] 0.815 (0.64 -1.03) *p* <0.01 [f] 0.648 (0.51 -0.81) *p* <0.01 [g] 0.255 (0.19 -0.35) |
| **9** | Liu et al. 2021[b] [66] | NG | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | *p* =0.015 OR 3.11 (1.24 -7.81) *p* =0.032 OR 2.86 (1.10 -7.48) | N/A |

*p* value is given first, followed by Odds ratio (95% Confidence Level) – OR (95% Cl) or r- value (Pearson correlation coefficient). Only significant associations are presented.

BMI: Body mass index, HDL: High Density Lipoprotein, MetS: Metabolic Syndrome, N/A: Not available, PWV: Pulse Wave Velocity, TG: triglyceride, UBC: Urinary BPA concentrations, OH-PAHs: hydroxylated polycyclic aromatic hydrocarbons (2-OH-FLU: 2-hydroxyfluorene, 1-OH-PHE: 1-hydroxyphenanthrene)

[a] OR adjusted for age, gender and nutritional status.

[b] OR adjusted for age (years), gender, and BMI (kg $m^2$). First OR value is for 2-OH-FLU is given, followed by 1-OH-PHE

[c] OR for current and past smokers.

[d] Overall hazard ratio (95% Confidence level) for metformin therapy.

[e] Hazard ratio for 1$^{st}$ (<25.3 months) tertile of metformin therapy.

[f] Hazard ratio for 2nd (25.3 – 57.3 months) tertile of metformin therapy.

[g] Hazard ratio for 3$^{rd}$ (57.3 months) tertile of metformin therapy.

[h] Findings in patients with polycystic ovaria syndrome (PCOS).

A total of 44,219 individuals were eligible to be included in the studies to evaluate which factors increased risk of developing nodular goiter. All studies presented the gender distribution of the total number of individuals included. In the case of Karaköse et al, only females were included as the study was focusing on how PCOS is associated with NG. From the data provided, 20,118 women and 24,101 men were included [5,49,54–56,58,63,64,66]. The mean age of all patients in the chosen studies was 50.81 years old [5,49,54,56,58,63,64,66].

Of the 44,219 individuals, 2,027 people had nodular goiter. Table 7 demonstrates the demographic characteristics of the individuals with NG included in the studies. All excluding Kir et al. and Tseng et al. demonstrated a predominance in women. Both studies did not include the distribution of males and females with NG [58,64]. The mean age of those affected by NG was older than the total study population [5,49,56,66].

Ovadia et al. studied the relationship between thyroid disease and low dietary intake of iodine in the Israeli adult population. They found a significant prevalence of elevated triglyceride serum levels (>60ng/ml) and low iodine intake (60 $\mu$g/d $\pm$ 30) in nontoxic nodular goiter subjects in comparison to the hypothyroidism and control groups [5].

Rendina et al. focused on the relationship between NG prevalence, smoking and its cessation. Smoking was established as an independent risk factor for simple NG, with both previous and current smoking increasing risk (OR 1.65 (95% Cl: 1.28–2.12), p<0.01 and OR 1.31 (95% Cl: 1.21–1.58), p<0.01) respectively. They also found that age, female sex, BMI, parity and MetS were associated with a significant increase in NG prevalence (OR 1.05 (95% Cl: 1.02-1.09), OR 1.91 (95% Cl: 1.51-2.30), (OR 1.51 (95% Cl:1.21–1.87), OR 1.98 (95% Cl: 1.52–2.31) and OR 1.34 (95% Cl: 1.11–1.67) respectively). Whereas alcohol had a significantly inverse relationship with incidence (OR 0.78 (95% Cl: 0.70–0.85) [49].

Karaköse et al. explored the effect of metabolic parameters and hormones of PCOS patients had on the incidence of NG in a case control study. They concluded that insulin resistance is a risk factor for both TN formation and TV. The results showed that the TNs were significantly associated with older age (p =0.001), BMI (p < 0.001), increased fasting glucose (p <0.005), and fasting insulin (p <0.004). Similarly, TV was significantly correlated with age (r =0.172, p =0.026), BMI (r =0.330, p <0.001), fasting insulin (r =0.212, p =0.006) and fasting glucose (r =0.195, p =0.012). They determined that NG incidence and TV were increased in PCOS patients, leading them to recommend that future PCOS patients should be assessed for NG [54].

Kir et al. evaluated the association of potential factors with thyroid nodularity in euthyroid subjects. During the study, multivariate analysis revealed that the only factor influencing the presence of NGs was older age (OR 1.05 (95% CI:1.03-1.07), $p$ <0.001) [58].

Zhou et al. investigated the relationship between excess iodine intake and bisphenol A levels with the development of NG and PTC. Multivariate regression analysis determined that age, higher UBC levels and iodine intake are significant risk factors for development of NG (OR 1.12 (1.08–1.17), OR 6.15 (2.16-17.53) and OR 4.93 (1.17–12.10) respectively) [55].

Aydoğan et al. used pulse wave analysis (PWA) to investigate whether the presence of insulin resistance, nodules and nodule stiffness have an effect on arterial stiffness – a known, reliable indicator of cardiovascular risk. The study revealed that in euthyroid NG subjects; PWV and fasting plasma glucose (FPG) were significantly increased ($p < 0.001$ and $p = 0.03$ respectively), suggesting a cardiovascular risk. A positive correlation was found of PWV with FPG and waist circumference ($p < 0.001$) [56].

Mayers et al. conducted a case-control study to assess she relationship between MetS and thyroid nodular disease in an iodine-sufficient area. Multivariate analysis revealed a positive association between the presence of TNs and Mets, low HDLs and impaired FPG (OR 2.96 (95% Cl: 1.47-5.95, $p < 0.05$), OR 2.77 (95% Cl: 1.44-5.3, $p < 0.05$) and OR 2.23 (95% Cl: 1.14-4.34, $p < 0.05$) respectively) [50].

Tseng et al. performed a population-based study to investigate how the risk of developing benign NG in T2DM patients is affected by metformin use. They used hazard ratios to reflect risk of development. The results revealed that metformin therapy reduced risk of benign NG; the overall hazard ratio was 0.527 (95% Cl: 0.447–0.621), with risk lowering with longer exposures of metformin (see table 7). However, they did conclude that it is too early to implement metformin use into treatment or prophylaxis of thyroid disorders [64].

Liu et al. investigated the risk of NG caused by exposure to hydroxylated polycyclic aromatic hydrocarbons (OH-PAHs). The study showed a higher NG risk associated with higher tertiles of 2-OH-FLU (OR 3.11 (1.24 -7.81), p =0.015) and 1-OH-PHE (OR 2.86 (1.10 -7.48), p =0.032), with a gender-specific increased risk with high tertiles of other types of PAH in women (1-OH-NAP, 2-OH-NAP, 2-OH-DBF, and 3-OH-FLU). [66]

**Table 9: Independent risk factors associated with Multinodular Goiter**

| | Author | Older age | Female sex | BMI | Alcohol | Smoking (previous or current) | Parity | MetS | SBP (> 140/90 mmHg) | Abdominal adiposity | Abnormal glucose metabolism |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | Rendina et al 2012 [28] | *p* = 0.005 OR 1.049 (1.017-1.086) | *p* = 0.007 OR 1.881 (1.424-2.471) | *p* = 0.019 OR 1.507 (1.207-1.871) | *p* = 0.031 OR 0.804 (0.698-0.918) | *p* = 0.023 OR 1.454 (1.267-1.649) | *p* = 0.009 OR 1.648 (1.424-1.819) | *p* = 0.021 OR 1.409 (1.109-1.789) | N/A | *p* = 0.002 [a] OR 1.551 (1.181-2.037) | *p* = 0.032 [a] OR 1.435 (1.026-2.050) |
| **2** | Kir et al 2018 [58] | *p* <0.001 OR 1.05 (1.03–1.07) | N/A | N/A | N/A | N/A | N/A | *p* <0.001 OR 1.87 (1.25–2.79) | *p* <0.008 OR 1.01 (1.0–1.02) | N/A | N/A |

*p* value is given first, followed by Odds ratio (95% Confidence Level) – OR (95% Cl). Only significant associations are presented.

MetS: Metabolic Syndrome, N/A: Not available, SBP: Systolic Blood Pressure

[a] Results of 2nd multivariate model that omitted 'BMI' and 'occurrence of MetS'. OR adjusted for age, gender, body mass index, nicotinism, parity, alcohol intake, thyroid function, and metabolic syndrome-related pharmacological treatment.

A total of 2,854 individuals were eligible to be included in the studies to evaluate which factors increased risk of developing multinodular goiter. Both studies presented the gender distribution of the total number of subjects included, revealing a female predominance. The mean age of the patients in the chosen studies was 57.35 years old [28,58].

Within the study investigating factors associated with thyroid nodularity, Kir et al. established a correlation between older age and MetS and MNGs via multivariate analysis ($p<0.001$). The study used the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) criteria to establish the presence of MetS. Subjects were identified with MetS if they met 3 out of 5 NCEP-ATP III criteria, MetS components included: WC, HDL, TG and SBP. Of the 673 non-toxic MNG subjects, 259 (61.5%) had MetS (OR 1.87 (95% CI:1.25–2.79), $p<0.001$). Furthermore, analysis revealed that SBP was the only MetS component that was an independent risk factor of MNG *(*OR 1.01 (95% CI:1.0–1.02), $p$ <0.008), irrespective of age [58]. See Table 9.

Rendina et al. investigated the relationship between MetS and MNG in euthyroid subjects living in areas of moderate iodine deficiency. Presence of MetS was defined using the American Heart Association/ National Heart, Lung and Blood institute criteria. The study used multivariate logistic regression analysis that confirmed that independent factors significantly associated with clinical evidence of non-toxic MNG were: age, female sex, BMI, parity, smoking (current or previous) and MetS (OR 1.049 (95 % CI: 1.017-1.086), $p$ = 0.005; OR 1.881 (95 % CI: 1.424-2.471), $p$ =0.007; OR 1.507 (95 % CI: 1.207-1.871), $p$ = 0.019; OR 1.648 (95 % CI: 1.424-1.819), $p$ = 0.009; OR 1.454 (95 % CI: 1.267-1.649), $p$ = 0.023; OR 1.409 (95% CI:1.109-1.789), $p$ =0.021 respectively). Whereas alcohol intake was inversely related to non-toxic MNG prevalence (OR 0.804 (0.698-0.918), $p$ = 0.031) [28].

A second multivariate analysis was conducted to assess the role of individual components of MetS on MNG that adjusted for age, gender, thyroid function, TSH levels, high serum TG, low HDL, hypertension and MetS-related treatment, and omitted ‘BMI’ and ‘occurrence of MetS’. The results showed that both abnormal glucose metabolism and abdominal adiposity are significant independent predictors of increased MNG risk (OR 1.435 (1.026-2.050), $p$ = 0.032 and OR 1.551 (1.181-2.037), $p$ =0.002 respectively). As seen in table 9 [28].

## 11.2 Risk factors in Nodular goiter associated with malignancy

**Table 10. Characteristics of included studies regarding malignancy risk factors in individuals with nodular goiter**

| No | Author | Country | Study type | Sample size | [a] Mean age | Aim of study |
|---|---|---|---|---|---|---|
| **1** | Lasithiotakis et al. 2012 [68] | Greece | Retrospective | 1,161 | 49.25 ± 14.89 | To evaluate prevalence and outcome of thyroid cancer among patients who underwent total thyroidectomy for diffuse MNG |
| **2** | Luo et al. 2012 [69] | USA | Retrospective | 1791 | 51.14 ± 1 | To identify risk factors for malignancy in patients with MNG |
| **3** | Kelly et al. 2017[70] | Ireland | Retrospective | 293 | 53.72 | To identify whether lesions within a multinodular goiter (MNG) without suspicious features can be followed with ultrasound rather than biopsied |
| **4** | Ajarma et al. 2020 [71] | Jordan | Retrospective | 600 | 44.3 ± 14.5 | To investigate if MNG is associated with a lower risk of malignancy compared to STN |
| **5** | Apostolou et al. 2020 [72] | Serbia | Prospective | 3233 | 56.4 | To evaluate the prevalence of thyroid cancer in patients operated on for MNG, and to determine risk factors for incidental thyroid malignancy |

[a] Mean age (±SD)

MNG: Multinodular goiter, NG: nodular goiter, PTC: Papillary thyroid cancer, STN: solitary thyroid nodules

**Table 11. Independent risk factors associated with thyroid carcinoma in Nodular Goiter patients**

| | Author | | Age | Male sex | Female sex | Functional thyroid status | Nodule size | Nodule number | Preop impression of malignancy | Histological thyroiditis | Suspicious US | Adenoma size | Thyroid gland size | HT | CNST | BMI | Urban area residence |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Lasithiotakis et al. 2012 [a] [68] | MNG | *p* =0.06<br>OR 0.98<br>(0.95–1.001) | N/A | N/A | N/A | N/A | N/A | N/A | *p* =0.09<br>OR 2.1<br>(0.9–4.8) | *p* =0.03<br>OR 2.3<br>(1.1–5.4) | N/A | N/A | N/A | N/A | N/A | N/A |
| 2 | Luo et al. 2012 [69] | MNG | *p* <0.001<br>OR 0.97<br>(0.960 -0.987) | N/A | *p* <0.001<br>OR 0.40<br>(0.251- 0.647) | N/A | *p*= 0.002<br>OR 0.81<br>(0.711-0.930) | *p* <0.001<br>OR 0.866<br>(0.809 -0.908) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| 3 | Kelly et al. 2017 [b] [70] | MNG | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | *p* <0.001<br>OR 38.359<br>(10.374–141.837)<br>*p* =0.042<br>OR 3.197<br>(1.145–63.983)<br>*p* =0.017<br>OR 6.888<br>(1.417 -33.475) | N/A | N/A | N/A | N/A | N/A | N/A |
| 4 | Ajarma et al. 2020 [71] | MNG | N/A | *p* <0.001<br>OR 2.792<br>(1.600–4.874) | N/A | N/A | N/A | N/A | *p* <0.001<br>OR 244.5<br>(77.6–770.5) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| 5 | Apostolou et al. 2020 [c] [72] | MNG | N/A | N/A | *p*= 0.001<br>OR 0.73<br>(0.60-0.88) | *p* <0.001<br>OR 0.68<br>(0.59-0.80) | N/A | N/A | N/A | N/A | N/A | *p*= 0.012<br>OR 0.99<br>(0.98 -1.00) | *???* | *p* <0.001<br>OR 2.31<br>(1.85 -2.89) | *p* <0.001<br>OR 2.54<br>(1.97 -3.26) | N/A | N/A |

*p* value is given first, followed by Odds ratio (95% Confidence Level) – OR (95% Cl). Only significant associations are presented.

BMI: Body mass index, CNST: Chronic non-specific thyroiditis, HT: Hashimoto's thyroiditis

[a] OR value for tumours with a diameter greater than 2cm

[b] OR values for US findings presented in the order of echogenicity first, followed by irregular margins and microcalcifications

[c] OR value for all thyroid cancers

[d] OR value for papillary thyroid carcinoma

Lasithiotakis et al. performed a retrospective study on diffuse MNG patients to determine independent risk factors for cancer incidence. Multivariate logistic regression analysis showed an independent association between younger age (OR 0.98 (95% Cl: 0.95 -1.00), *p*= 0.06), histological thyroiditis (OR 2.1 (95% Cl: 0.9 -4.8), *p* = 0.09) and US findings (OR 2.3 (95% Cl: 1.1 -5.4), *p* = 0.03), with the prevalence of cancers with a diameter bigger than 2 cm [68].

Luo et al. conducted a study on 838 MNG patients that had undergone a thyroidectomy, in order to establish risk factors that can be used as malignancy predictors. Independent risk factors for malignancy identified via multivariate analysis included younger age, smaller nodule size and fewer nodules (OR 0.97 (95% Cl: 0.960 -0.987), *p* <0.01, OR 0.81 (95% Cl: 0.711 -0.930), *p* =0.002, and OR 0.866 (95% Cl: 0.809 -0.908), *p* <0.001 respectively). However, they concluded that age would not be a strong independent predictor of malignancy, due to its odds ratio approaching a value of 1 that implies it wouldn't be useful in predicting risk. Both nodule size and number were negatively correlated with malignancy, as the malignant group had fewer nodules (smaller percentage of ≥5 nodules – 20.9% vs 42.6%) and their largest nodules were smaller in size compared to the non-malignant group (2.32cm vs 3.05cm). Male gender was also identified as an independent predictor, with its percentage being higher in the malignant group compared to the non-malignant group (*p* <0.01; 28% vs 17%) [69].

Kelly et al. investigated how suspicious sonographic findings could be used for risk stratification of neoplasia. They found that the presence of ≥1 suspicious features significantly increases neoplasia risk (*p* <0.001). Multivariate analysis results determined that sonographic findings independently associated with malignancy were heterogeneous echogenicity (OR 38.359 (10.374–141.837), *p* < 0.001), irregular margins (OR 3.197 (1.145–63.983), *p* =0.042), and microcalcifications (OR 6.888 (1.417 -33.475), *p* =0.017) [70].

Ajarma et al. evaluated factors in MNG patients associated with incidence of thyroid carcinoma. Multivariate analysis results identified male gender (OR 2.792 (95% Cl: 1.600–4.874), *p* <0.000005) and preoperative impression of malignancy by US, FNAC or clinical findings (OR 244.5 (95% Cl: 77.6–770.5), *p*= 0.000082) as significant risk factors that can be used for predicting thyroid malignancy [71]. Leading to the recommendation that thyroid nodules should be routinely assessed by US.

Apostolou et al. conducted a prospective study to investigate risk factors for incidental thyroid cancer in patients who underwent a thyroidectomy for benign MNG. Multivariable regression analysis was used to determine independent variables associated with thyroid malignancy risk. Results demonstrated that smaller adenoma size, Hashimoto's thyroiditis and chronic non-specific thyroiditis independently increase risk (OR 0.99 (95% Cl: 0.98 -1.00), OR 2.31 (95% Cl: 1.85 -2.89), and OR 2.54 (95% Cl: 1.97 -3.26)) respectively. Younger age, male sex (27.5% increased risk) and smaller thyroid gland size were also identified as independent risk factors. Whereas as female gender (OR 0.73, 0.60 to

0.88; p =0.001) and functional thyroid status (OR 0.68 (95% Cl: 0.59-0.80), $p$ <0.01) were associated with decreased malignancy risk [72].

# 12. DISCUSSION

**Main findings:**

The purpose of this systematic review was to determine which factors were associated with NG and could be independent predictors of the disease in the general population and for malignancy. A literature search was performed using various databases and a total of 28 studies were selected to be included in this review. The chosen studies focus on either NG, TN, TV or goiter in different study populations to gain a more thorough understanding of which factors contribute to the pathogenesis of the disease.

The study populations demonstrated that incidence of TNs and NG is higher in females, with subjects being older than the total population (see tables 3 and 7). The small ratio of male to female subjects and age disparity in the studies are congruent with the established knowledge that age and female gender significantly influence NG incidence. Although the majority of studies excluded age and gender as confounding factors in their regression models, the small number of male participants does weaken the power of the studies [5,47,48,56,63,65,66].

Based on results of table 4, the most common factors independently associated with increased risk of TNs are age ($p < 0.001$), female sex ($p < 0.001$) and BMI ($p < 0.05$). With Fan et al. reporting risk had significantly increased with each age decade upon stratification [47,50–53,57,59,60,65]. Concerning lifestyle factors, smoking was determined as an independent risk factor for TNs by Feng et al. and Jiang et al. and for TV by Aydin et al. and Dauksiene et al. [47,50,51,53]. While Chen et al. stated alcohol significantly reduced risk [65].

4 articles evaluated the influence of MetS or its individual clinical parameters on TN incidence, and 5 studies investigated the relationships with TV [48,50,59,61,62]. MetS components include hypertension, IFG or a previous T2DM diagnosis, increased TG levels, low HDL, and abdominal obesity that is determined either by WC or BMI >30kg/$m^2$. All 4 articles found that MetS significantly increased TN risk, with Su et al. and Guo et al. both reporting a significant independent association with both TNs and TVs. Only 1 MetS component was found to independently increase risk by Su et al. (WC) and Guo et al. (elevated SBP), whereas Feng et al. listed elevated WC, IFG and SBP. Furthermore, Su et al. established that WC was an independent predictive factor for both TNs and TV, and HDL a protective factor. Concerning TV prevalence, Guo et al. recognised elevated SBP, abdominal adiposity and hypertriglyceridemia to be independent factors. Whilst Anil et al. confirmed both WC and T2DM [48,50,59,61,62].

9 articles focused on NG in general populations or specific patient groups (PCOS and T2DM). Ovadia et al. determined that elevated TG serum levels and low dietary iodine intake were positively associated with NNG in the Israeli adult population [5]. Rendina et al. established age, female sex, BMI, parity and MetS, in addition to both previous and current smoking as independent risk factors and alcohol as a protective factor for simple NG. Conversely, Kir et al only confirmed older age [49,58]. Zhou et al.

determined that age, higher UBC levels and excess iodine intake are significant risk factors [55]. Whilst Liu et al. determined that higher exposures to hydroxylated PAHs such as 2-OH-FLU and 1-OH-PHE increased NG risk, with other types affecting risk in women only [58].

Aydoğan et al. found that euthyroid NG subjects have a higher PWV that is positively correlated with fasting glucose and WC. Leading to the notion that individuals with NG are at increased risk of cardiovascular disease [56]. Mayers et al. found that in iodine-sufficient areas, TNs are significantly associated with MetS, low HDLs and impaired FPG [50]. In PCOS patients, Karaköse et al. determined that older age, BMI, increased fasting glucose and insulin were risk factors for both TN formation and TV [54]. These led to the conclusion that insulin resistance is involved in increased NG prevalence [54,63]. Whilst in T2DM patients, metformin therapy reduced risk of benign NG; with risk lowering with longer exposures of the drug [64].Whilst the data findings of Karaköse et al. and Tseng et al. cannot be applied to the general population as they focused on specific populations, their results were included to gain a comprehensive understanding on the relationship of life style factors and NG prevalence.

Rendina et al. confirmed that age, female sex, BMI, parity, previous or current smoking, MetS, abnormal glucose metabolism and abdominal adiposity are significant independent predictors of increased non-toxic MNG risk. Whereas alcohol intake had an inverse relationship to prevalence [28]. Kir et al. found that significantly increased MNG risk was correlated to older age and MetS, with SBP being the only MetS component to independently increase risk [58].

5 articles assessed the association between MNG factors and malignancy risk. Lasithiotakis et al. determined that younger age, histological thyroiditis and US findings were independent risk factors for cancers with a diameter >2 cm [68]. Luo et al. established younger age, smaller nodule size, fewer nodules and male gender as independent predictors of malignancy [69]. Whilst Kelly et al. confirmed the presence of ≥1 suspicious features on US and Ajarma et al. identified male gender and preoperative impression of malignancy as significant risk factors [70,71]. Apostolou et al. determined smaller adenoma size, Hashimoto's thyroiditis, CNST, younger age, male sex and smaller thyroid gland size increase risk, whilst female gender and functional thyroid status decrease malignancy risk [72].

**Strengths of the review**

The preponderance of studies included multivariate regression analysis to analyse their results and determine independent predictors of NG [58,63], nodules [48,52,53,57,59,62,67], goiter [47,48,53,62] and malignancy [68–72]. Multivariate models were used to remove possible confounding factors by considering the contributions of other variables in the final outcome. Furthermore, only significant associations found in the research were mentioned in this review; a p value <0.05 was considered statistically significant. Another advantage of some studies was the extensive characterisation of patient

phenotypes, including their metabolic characteristics, thyroid function (FT4, TSH, TPOAb) and anthropometric measurements [28,48,49,53,56,57,59,60,62,65].

**Limitations of the review**

This systematic review encountered several limitations. Firstly, the data collected was limited to articles written in the English language and had full-text freely accessible, so it could be argued that not all relevant data was obtained. Secondly, the chosen articles were predominantly of a retrospective design, with few noting that the future studies should be conducted prospectively to strengthen them [48,63].

Another limitation was that several authors conducted their studies in a cross-sectional design. So, in the cases of Rendina et al. and Ovadia et al., no causal links could be definitively established between NG development and factors [49]. Only assumptions or predictions could be made. In the case of Guo et al., Buscemi et al., Moon et al., Chen et al., Jiang et al., and Song et al., they could not confirm the etiological relationships of thyroid nodule incidence and presence of factors [51,52,59,61,65]. The small sample sizes of some the studies may have also precluded a variety of associations [66].

As for articles pertaining to NG as a whole, the main constraint was concerning the chosen study populations. The data obtained by Rendina et al., Mayers et al., Ovadia et al. and Lasithiotakis cannot be extrapolated to reflect the findings of the general population as their study populations were relatively small, not randomised and in a hospital environment, thereby introducing possible statistical and selection bias [5,28,49,63,68]. These limitations made the interpretation of findings on an epidemiological basis difficult, restricting the extent to which the research question can be answered.

Thus, it is recommended that future prospective studies, with large randomised study populations and longer follow-up periods are carried out to strengthen the findings on the relationship between the disease and its contributing factors [63,64,66]. An additional recommendation is to stratify age into separate groups [62].

**Other systematic reviews**

The results of this review are consistent with findings presented in other systematic reviews. Simsir et al. published a systematic review on factors associated with NG and PTC, noting that IR, MetS and obesity play important roles in increasing NG prevalence and thyroid cancer [31]. Knudsen et al. conducted a review on how genetic and environment factors unrelated to iodine contribute to NG. They concluded that smoking was a risk factor with its effect modifiable by iodine intake. Whilst IR and childbirth increase risk of goiter, oral contraceptives play a protective role and metformin therapy can reverse risk of goiter [37]. In regards to malignancy risk factors, Campbell et al., Syrenicz et al. and Nixon et al. also confirmed male sex, younger age and suspicious US findings, in addition to symptoms of airway compression, family history, and history of head and neck radiation [2,10,11].

# 13. CONCLUSION

In conclusion, the review found great disparity in the prevalence of NG between chosen study populations (varying from 1.53% to 50%). Although the findings of some of these study populations could not be extrapolated to reflect the findings of the general population, all included studies did demonstrate similar demographics. NG is more predominant in females, with the mean age of individuals affected being older than the total study population.

Results demonstrated that age, female sex, smoking, MetS and its individual components, higher education, physical labour and milk consumption were associated with nodule and/or goiter formation. Whilst HDL levels and alcohol reduce the risk of nodule development.

Both non-modifiable risk factors such as age, and female sex, and modifiable factors like BMI, parity, MetS, low HDLs, impaired FPG, previous and current smoking independently increase risk of NG and MNG. Prevalence of NG is also found to be significantly associated with higher exposures to hydroxylated PAHs such as 2-OH-FLU and 1-OH-PHE. Elevated TG serum levels (>60ng/ml) and low dietary iodine intake (60 $\mu$g/d + 30) were positively associated with NNG in Israeli adults. In Turkey, euthyroid NG subjects have a higher PWV that is positively correlated with fasting glucose and WC. Whereas alcohol consumption plays a protective role against NG.

In PCOS patients, IR is involved in increased NG prevalence, specifically increased fasting glucose and insulin in TV and nodule development. Longer exposure to metformin therapy in T2DM patients, reduces risk of benign NG.

In patients with MNG: younger age, male gender, preoperative impression of malignancy via suspicious features on US, FNAC or clinical examination are independent predictors of malignancy. Smaller nodule size, fewer nodules, smaller adenoma size, histological thyroiditis, Hashimoto's thyroiditis, CNST and smaller thyroid gland size also increase malignancy risk, whereas female gender and functional thyroid status decrease risk.

Very few large-scale population-based studies regarding NG have been performed, and as their cross-sectional design do not reflect a true representation- the data on how the general population are affected by NG is still lacking. It is recommended that future prospective studies, with large randomised study populations and longer follow-up periods are carried out to reflect the effects of risk factors on NG on the whole population, rather than specific study populations. Furthermore, stratifying age into separate groups in future studies will also help strengthen the findings on the exact relationship between the disease, its contributing factors and malignancy risk, whilst eliminating bias.

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