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REVIEW ARTICLE

Obesity and thyroid cancer: unraveling the connection through a systematic review and meta-analysis of cohort studies

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Abstract

Background The relationship between adiposity indicators and thyroid cancer (TC) risk has garnered increasing attention due to the rising prevalence of obesity and its potential impact on cancer incidence. We conducted a comprehensive meta-analysis to investigate this association across various effect measures.

Method Until July 2022, a comprehensive search of databases was conducted to identify cohort studies that assessed the association between adiposity and the development of TC. Meta-analysis was performed using random effects models. Subgroup analyses were conducted to explore heterogeneity. Publication bias was assessed using Begg's tests.

Results A systematic literature search identified 27 eligible studies reporting odds ratios (OR), relative risks (RR), or hazard ratios (HR) as effect measures. Pooling the studies irrespective of the effect measure, a significant positive association between adiposity indicators and TC risk was observed, yielding an effect estimate of 1.16 (95% CI 1.12–1.21). The combined effect estimate for OR/RR studies was 1.10 (95%CI 1.04–1.17), while HR studies yielded an effect estimate of 1.20 (95%CI 1.13–1.26). Subgroup analyses revealed associations across different age groups, obesity indices, and regions, with some variations based on effect measure. Meta-regression identified follow-up duration as a confounding factor only in HR studies.

Conclusion The synthesis of 27 studies with diverse designs and populations underscores a robust positive association between adiposity and TC risk, providing compelling evidence for the potential role of increased adiposity in TC development.

Keywords Adiposity · Thyroid cancer · Cohort study · Obesity

Introduction

While thyroid cancer stands as the most common form of endocrine cancer, it is a comparatively uncommon malignancy, representing a mere 4% of global cancer cases according to GLOBOCAN 2018 statistics [1]. Furthermore, Asia is the region where 60% of all instances take place [1]. The increasing occurrence of thyroid cancer worldwide over the past decades [2], coupled with consistent mortality rates, implies that the adoption of novel diagnostic methods like ultrasonography, computed tomography, and magnetic resonance imaging, along with improved healthcare accessibility, has led to the identification of asymptomatic cases which are primarily response for the observed rise [3]. Other factors could also have an influence, including alterations in exposure to environmental elements [4].

Obesity stands as the second most prevalent avoidable and adjustable contributor to cancer development, following

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smoking [5]. The burden of cancer cases linked to obesity, represented by the population attributable fraction (PAF), accounts for 11.9% in males and 13.1% in females for all cancers linked to obesity. This percentage exhibits global diversity, linked to distinct obesity occurrence rates in various regions [6]. While obesity is acknowledged as a recognized risk element for cancer development, it appears to exert varying influences on different cancer types.

Adipose tissue functions as an active endocrine organ, capable of producing and releasing numerous hormones, adipokines, and growth factors. These substances can disrupt the normal processes of cell growth and survival, thereby contributing to the progression of cancer [7].

The existing data concerning the relationship between these two conditions have yielded conflicting results [8, 9]. In the majority of instances, the discrepancies arise from the diverse approaches used to assess the status of obesity. Various indicators have been utilized, including measures like visceral adipose tissue, waist circumference, waist-to-hip ratio, subcutaneous adipose tissue, and BMI.

Establishing evidence of a potential unfavorable impact of obesity on thyroid cancer holds significance for clinical interventions. This entails putting weight reduction initiatives into action and formulating thyroid cancer screening recommendations that are specifically designed for individuals who are overweight or obese. Hence, we conducted a comprehensive systematic review and meta-analysis of observational cohort studies to examine the relation between different indicators of adiposity and the risk of thyroid cancer. (i) We evaluated the shape of the dose–response relation between BMI and thyroid cancer by utilizing restricted cubic splines models; (ii) we employed subgroup and meta-regression analyses to assess potential origins of heterogeneity, encompassing factors related to etiological diversity, methodological attributes, and factors that modify the effects.

Materials and methods

Literature search and inclusion criteria

We conducted an extensive literature review by searching databases including PubMed, Scopus, EMBASE, Web of Science, and Google Scholar, until July 2022. The search terms for adiposity included body mass index, BMI, Quetelet index, body weight, overweight, obesity, obese, adiposity, anthropometry, body composition, body fat distribution, body fat patterning, waist circumference, hip circumference, waist-to-hip ratio, retroperitoneal fat, visceral fat, abdominal fat and intra abdominal fat. Those terms were combined with search terms for thyroid cancer including thyroid carcinoma, thyroid cancer, thyroid neoplasms and thyroid tumour. Our literature search was restricted to human studies published in the English language. Studies were deemed potentially suitable if they met the following criteria: (i) were original observational studies; (ii) possessed a prospective or retrospective design; (iii) explored the link between BMI, weight, waist circumference, hip circumference, or waist-to-hip ratio and thyroid cancer; (iv) provided data on relative risks (RRs), hazard ratios (HRs), or odds ratios along with their corresponding 95% confidence intervals (CIs). For inclusion in the dose-response analysis, studies were needed to encompass at least three BMI categories.

Cross-sectional studies, literature reviews, case-control studies, animal or genetic variation studies, and studies without reporting TC events in the subgroups were excluded from consideration.

All the articles included in the study were published in English. The process of selecting these studies is depicted in Fig. 1. The systematic review was carried out in accordance with the guidelines laid out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [10]. Registration code of the systematic review and meta-analysis protocols in PROSPERO is CRD42023459009.

Study selection

Following the removal of duplicates, two authors (BA and FA) independently assessed the titles and abstracts derived from the initial search. Both authors (BA and FA) reviewed the full-text articles to ensure they met the criteria for inclusion and exclusion. In cases of disagreements, a third author (ARA) reevaluated the issues.

Data extraction and quality assessment

Data extraction was independently carried out by two reviewers (BA and FA), and any disparities were resolved through consensus. We extracted information about the first author, year of publication, country, study design, follow-up duration, population, age, number of participants, sex, adiposity index, thyroid cancer histologic type. Only fully adjusted effect estimates, as reported in the studies, were extracted and subsequently incorporated into the meta-analysis.

The Newcastle-Ottawa Scale (NOS), a tool designed for assessing nonrandomized studies in systematic reviews and meta-analyses, was employed [11]. The NOS comprises eight items that are divided into three categories: selection, comparability, and exposure. Each item within the NOS offers response choices. The star system is employed to semi-quantitatively evaluate the quality of the studies,

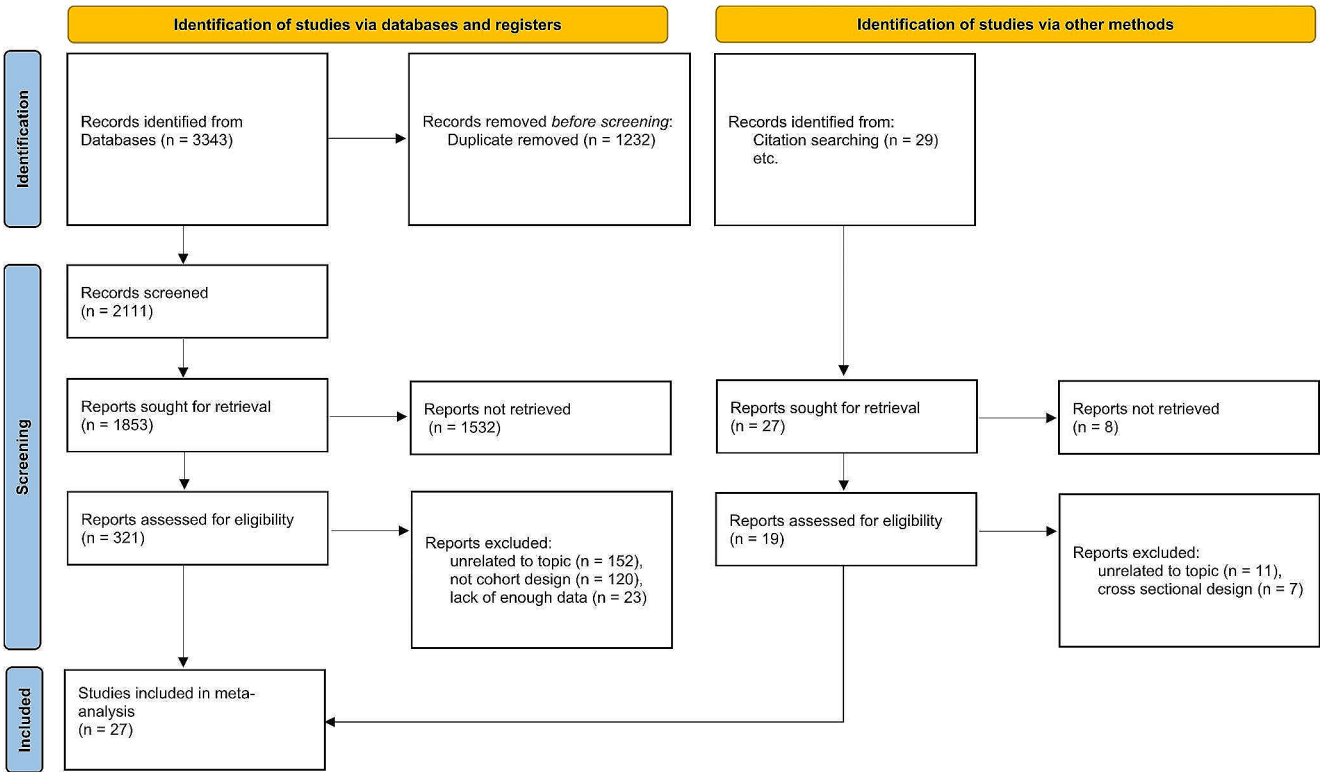

Fig. 1 PRISMA flow diagram for selection process of the studies

assigning a maximum of 1 star per item to the highest quality studies. However, in the case of evaluating comparability, an exception is made where 2 stars can be awarded. Thus, the NOS operates on a scale from 0 to 9 stars [12]. The specifics of data extraction and quality assessment are outlined in Table 1.

Statistical analysis

All statistical analyses were conducted using Stata, version 17.0 (Stata Crop, College Station, TX, USA). The effect sizes were combined using the random-effects method (Dersimonian-Laird) for the meta-analysis. In the subsequent analyses, we separated the pooling of studies that reported OR and RR from those reporting HR, in order to accommodate variations in study design and methodology. The I^2 index and Cochrane's Q test were utilized to evaluate the heterogeneity among the studies. The I^2 interpretation is as follow: low if $I^2 < 30\%$, moderate if $I^2 = 30–75\%$, and high if $I^2 > 75\%$. To address the heterogeneity among studies, subgroup analyses were conducted, stratifying by factors such as age, sex, obesity indices, and geographical regions. Meta-regression was employed to investigate the potential confounding effects of variables such as follow-up duration and age on the association. To ensure the robustness of the findings, publication bias was evaluated using Begg's test. The dose-response meta-analysis was executed employing restricted cubic splines models, aiming to elucidate the connection between different levels of adiposity and the risk of TC. For this purpose, a restricted cubic spline model with three knots was used. Thirteen studies were included in the analysis to investigate the dose-response relationship between BMI and TC using a one-stage random-effect model. The model was optimized using maximum likelihood estimation (LM).

Result

Search results

By conducting an initial search using keywords relevant to our topic, we identified a total of 3,343 full-text articles. After removing duplicate studies and applying the inclusion and exclusion criteria in two distinct stages (title and abstract review), we ultimately incorporated 27 eligible cohort studies in our review. Figure 1 provides an overview of the primary research outcomes and the process employed for selecting pertinent studies.

This meta-analysis included 27 articles and 28,354,187 participants in total [13–39] (Table 1).

Table 1 General characteristics of retrieved studies (presented in chronological order, starting with the most recent)

First author, year (Reference No)	Country	Study design	Follow up (years)	Population	Age	Number of participants	Sex	Adiposity index	Thyroid cancer histologic type	Study quality (NOS)
Park, 2022 [13]	South Korea	Prospective	NM	General population	51.5 ± 8.1	4658473	M, F	WC	Thyroid cancer	8
Nguyen, 2022 [14]	South Korea	Prospective	7.4	General population	52.82 ± 8.32	160650	M, F	BMI	Thyroid cancer	7
Ahmadi, 2022 [15]	USA	Prospective	3	General population	54.3 ± 15	1259	M, F	BMI	Thyroid cancer, papillary thyroid cancer, follicular thyroid cancer, medullary thyroid cancer, anaplastic thyroid cancer	6
Lee, 2020 [16]	South Korea	Retrospective	4.79	General population	NM	234786	M, F	BMI	Thyroid cancer	7
Park, 2020 [17]	South Korea	Prospective	7.2	General population	47.16 ± 13.09	9890917	M, F	WC	Thyroid cancer	8
Abdel-Rahman, 2019 [18]	Canada	Prospective	NM	Participants of PLCO trial	NM	147268	M, F	BMI	Thyroid cancer	7
Kwon, 2019 [19]	South Korea	Retrospective/ Prospective	NM/ 5.3	General population	50.1 ± 13.7	11323006/ 255051	M, F	BMI, WC	Thyroid cancer	8
Sado, 2017 [20]	Japan	Prospective	20	General population	51.86 ± 8	102723	M, F	BMI	Thyroid cancer, papillary thyroid cancer, follicular thyroid cancer	7
Al-Ammar, 2017 [21]	Saudi Arabia	Retrospective	5.2	Differentiated thyroid cancer patients	41.1 ± 11.6	209	M, F	BMI	Thyroid cancer, papillary thyroid cancer, follicular thyroid cancer, medullary thyroid cancer, anaplastic thyroid cancer	4
Son, 2017 [22]	South Korea	Prospective	7.01	General population	NM	351402	M, F	BMI	Thyroid cancer	6
Shin, 2016 [23]	South Korea	Prospective	5.3	General population	41.03 ± 9.78	141157	M, F	BMI	Thyroid cancer, papillary thyroid cancer, follicular thyroid cancer	6
Farfel, 2014 [24]	Israel	Prospective	40	Adolescents	16–19	478445, 1145865	M, F	BMI	Thyroid cancer, papillary thyroid cancer, follicular thyroid cancer, medullary thyroid cancer, anaplastic thyroid cancer	6
Bhaskaran, 2014 [25]	UK	Prospective	25	General population	NM	5243978	M, F	BMI	Thyroid cancer	7
Kitahara, 2012 [26]	USA	Prospective	10.1	Retired individuals	63.8 (51.3–72.1), 63.1 (51.3–71.9)	125347, 72363	M, F	WC, HC, WHR	Thyroid cancer	6
Kabat, 2012 [27]	USA	Prospective	11	Postmenopausal women	63 ± 7.2	144319	F	BMI, weight, WC, HC, WHR	Thyroid cancer, papillary thyroid cancer, follicular thyroid cancer, medullary thyroid cancer, anaplastic thyroid cancer	5
Rinaldi, 2012 [28]	France	Prospective	11.17	General population	52.3 ± 10.2, 50.9 ± 9.9	146824, 343765	M, F	BMI, WC, HC, WHR	Thyroid cancer	7

Table 1 (continued)

First author, year (Reference No)	Country	Study design	Follow up (years)	Population	Age	Number of participants	Sex	Adiposity index	Thyroid cancer histologic type	Study quality (NOS)
Almquist, 2011 [29]	Norway, Austria, and Sweden	Prospective	12	Participants of Metabolic syndrome and cancer project	43.9 ± 11.1, 44.1 ± 12.3	289866, 288834	M, F	BMI	Thyroid cancer	7
Kitahara, 2011 [30]	USA	Prospective	10.3	General population	mean: 58.18	848932	M, F	BMI	Thyroid cancer, papillary thyroid cancer, follicular thyroid cancer, medullary thyroid cancer, anaplastic thyroid cancer	7
Andreotti, 2010 [31]	USA	Prospective	12	Participants of Agricultural Health Study	NM	39628, 28319	M, F	BMI	Thyroid cancer	5
Clavel-Chapelon, 2010 [32]	France	Prospective	13.13	General population	55.5 ± 6.7	91909	F	BMI	Thyroid cancer, papillary thyroid cancer, follicular thyroid cancer	5
Leitzmann, 2010 [33]	USA	Prospective	7.2	Retired individuals	mean: 61.9	48436	M, F	BMI	Thyroid cancer, papillary thyroid cancer, follicular thyroid cancer, medullary thyroid cancer, anaplastic thyroid cancer	5
Meinhold, 2009 [34]	USA	Prospective	15.8	General population	NM	90713	M, F	BMI	Thyroid cancer, papillary thyroid cancer, follicular thyroid cancer	6
Song, 2007 [35]	South Korea	Prospective	8.75	Postmenopausal women	55.9 ± 5	170481	F	BMI	Thyroid cancer	5
Engeland, 2006 [36]	Norway	Prospective	23	General population	mean: 44	963523, 1037424	M, F	BMI	Thyroid cancer, papillary thyroid cancer, follicular thyroid cancer, medullary thyroid cancer, anaplastic thyroid cancer	6
Samanic, 2006 [37]	Sweden	Prospective	19	General population	mean: 34.3	362552	M	BMI	Thyroid cancer	6
Rapp, 2005 [38]	Austria	Prospective	9.93	General population	42.16 ± 15.12	145931	M, F	BMI	Thyroid cancer	7
Oh, 2005 [39]	South Korea	Prospective	10	General population	NM	781283	M	BMI	Thyroid cancer	7

Abbreviations M, F, male, female; NOS, Newcastle–Ottawa Scale; BMI, body mass index; NM, not mentioned; WC, waist circumference; HC, hip circumference; WHR, waist to hip ratio; PLCO, prostate, lung, colorectal and ovary trial

Study characteristics

Table 1 summarizes the diverse characteristics of included studies. The sample size of included studies ranged from 209 to 11,323,006 participants. Studies were conducted in South Korea [13, 14, 16, 17, 19, 22, 23, 35, 39], USA [15, 26, 27, 30, 31, 33, 34], Canada [18], Japan [20], Saudia Arabia [21], Israel [24], UK [25], France [28, 32], Norway [36], Sweden [37], Austria [38] and one of the cohorts were conducted in Norway, Austria, Sweden [29]. Follow-up duration ranged from 3 to 23 years. Twenty-one studies used BMI for diagnosis of obesity; two studies used the WC; one research examined WC, HC, WHR; and other three studies assessed BMI, WC, HC, WHR as adiposity indices. Twenty-two studies involved both sexes, but five researches conducted in females [27, 32, 35] or males [37, 39] only.

Pooled analysis of different effect measures of adiposity indicators and thyroid cancer risk

We conducted an extensive meta-analysis to explore the association between indicators of adiposity and the risk of thyroid cancer. Through a systematic literature search, we identified 27 eligible studies that reported a range of effect measures, including odds ratios (OR), relative risks (RR), and hazard ratios (HR).

When considering all studies collectively, regardless of the effect measure employed, the overall effect estimate yielded an effect estimate (OR/RR/HR) of 1.16 with a corresponding [95% confidence interval (CI) 1.12–1.21] (Fig. 2). This combined outcome emphasizes a notable and positive association between indicators of adiposity and the risk of TC. This underscores the potential role of increased adiposity in the progression of TC. Recognizing the distinct characteristics of these effect measures and their implications for interpreting associations, we adopted a stratified approach. We pooled studies separately based on the specific type of effect measure to enhance the accuracy of our findings. In subsequent analyses, we segregated studies reporting odds ratios (OR) and relative risks (RR) from those reporting hazard ratios (HR) to address disparities in study design and methodology. In the pooled analysis of studies reporting OR and RR, the combined effect estimate indicated an effect estimate (OR/RR) of 1.10 with a [95%CI 1.04–1.17], demonstrating a significant positive association between adiposity indicators and TC risk (Fig. 3). This finding supports the notion that higher adiposity may be associated with an increased likelihood of TC development. On the other hand, in the subgroup of studies reporting HR, the overall effect estimate (HR) was 1.20 with a 95%CI [1.13–1.26] (Fig. 4). This outcome implies that elevated levels of adiposity might contribute to a heightened risk of thyroid cancer incidence, thereby reinforcing the importance of the identified association.

Subgroup analysis

Significant statistical heterogeneity was observed among the included studies in the pooled analysis of adiposity and thyroid cancer development for studies reporting OR and RR (I^2 95.72%), as well as for studies reporting HR (I^2 93.81%). Consequently, we conducted subgroup analyses. Subgroup analyses of studies reporting OR/RR indicated a significant association between adiposity and the development of TC, in each subgroup based on age, obesity indices, and region (Europe and Asia, but not in America) (Table 2). However, in the subgroups based on sex, no significant association was observed (Table 2). Nevertheless, in subgroup analyses of studies reporting hazard ratios (HR), a significant association between adiposity and thyroid cancer development was evident within each subgroup categorized by age, sex, obesity indices, and region (America and Asia, but not in Europe) (Table 3).

Meta-regression

According to meta-regression (Table 4), the association between adiposity and the development of thyroid cancer was notably influenced by follow-up duration. This effect was significant only in studies reporting HR (Coefficient = -0.007, SE = 0.001, P-value < 0.001). However, in other instances, meta-regression did not identify any significant association between adiposity and thyroid cancer development in relation to age and follow-up duration.

Publication bias

Begg's test indicated no publication bias in all studies together ($P = 0.21$), studies reporting OR/RR ($P = 0.43$), and HR ($P = 0.09$) for the association between adiposity and TC development (see Supplementary Figs. 1, 2, and 3).

Dose–response meta-analysis of adiposity and risk of thyroid cancer

The chi-squared test statistic for the model was 72.36 (df = 2), with a P-value < 0.001, indicating that the model is statistically significant. The estimated effect of doses1 on the outcome was significant (exponentiated coefficient = 1.053842, $P < 0.001$). For each unit increase in dosese1, the outcome is expected to increase by a factor of approximately 1.053842. The estimated effect of doses2 on the outcome was also significant (exponentiated coefficient = 0.9780913, $P = 0.001$).

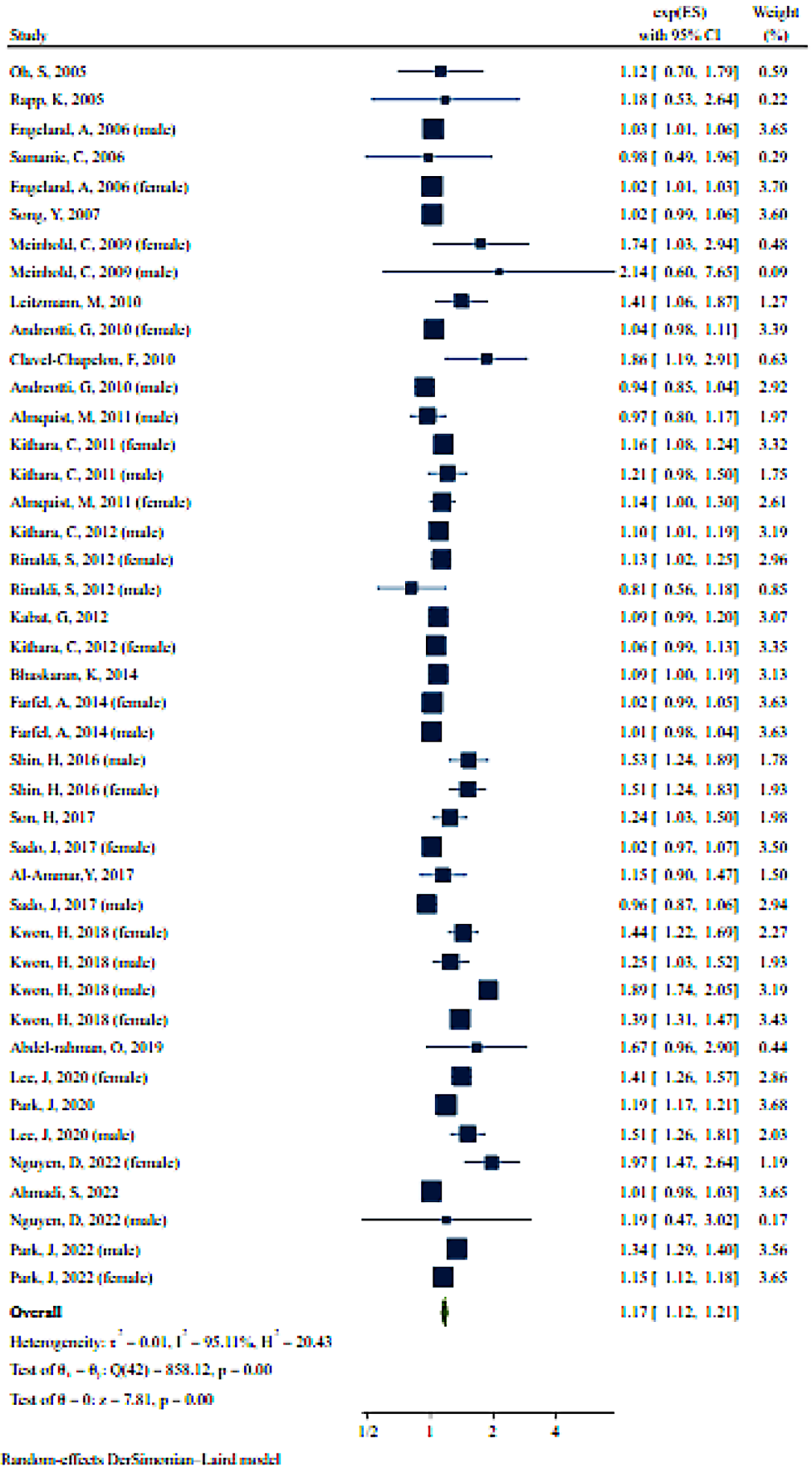

Fig. 2 Overall effect estimate of the association between indicators of adiposity and the risk of thyroid cancer

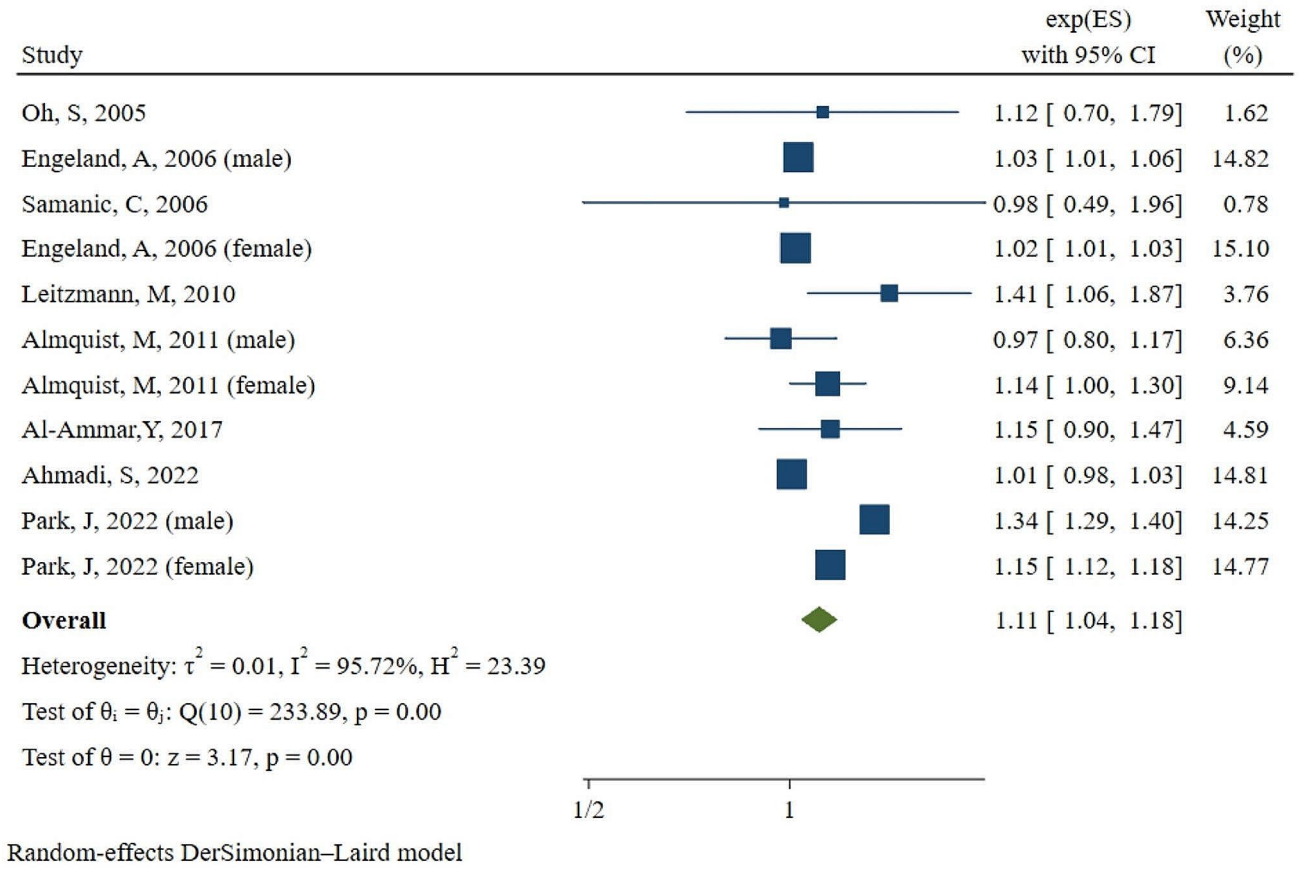

Fig. 3 Effect estimate (OR/RR) of the association between indicators of adiposity and the risk of thyroid cancer

for each unit increase in doses 2, the outcome is expected to decrease by a factor of approximately 0.9780913 (Fig. 5).

Discussion

The results from our meta-analysis, which investigated the connection between measures of adiposity and the occurrence of TC, add to the increasing pool of evidence concerning how obesity-related factors influence the risk of cancer. Our research compiled information from 27 qualifying studies, covering various effect measurements and geographical areas. The thorough examination produced a general effect estimate of 1.16, with a 95% confidence interval ranging from 1.12 to 1.21. This signifies a significant and positive correlation between adiposity indicators and the risk of thyroid cancer.

The existing data concerning the relationship between these two conditions have presented incongruous results [8, 9]. Numerous studies have reported on this relationship. In the study by Son et al. [40], an examination of information sourced from the Korean National Health Insurance Service (NHIS) was conducted on a substantial cohort ($n = 351,402$) of individuals in Korea who were over 20 years old. Based on the WHO criteria for Asians, around 30% of the participants were categorized as obese, and within this group, approximately 1% developed thyroid cancer following a median observation period of 3.9 years [41]. Kwon et al. [42] similarly conducted a retrospective assessment of 11,501,967 Korean individuals (aged ≥ 20 years) who were part of the NHIS database spanning from 2009 to 2012. The aim was to examine the relationship between BMI based on the WHO criteria for Asians, waist circumference, and the occurrence of thyroid cancer. Within this patient cohort, 25.7% were classified as overweight, 29.9% as obese, and 3.4% as severely obese. During a median duration of 4.39 years, a total of 50,464 individuals were diagnosed with thyroid cancer. In their study, Kitahara et al. [43] examined the associations between being overweight or obese and the rates of papillary thyroid cancer incidence using a substantial US database spanning the years 1995 to 2015. The risk of developing papillary thyroid cancer rose among individuals who were overweight [HR 1.26 (1.05–1.52)] and obese [HR 1.30 (1.05–1.62)], in comparison to those who had a normal weight, with a notably higher risk observed among individuals with class 3 obesity [HR 1.93 (1.15–3.22)].

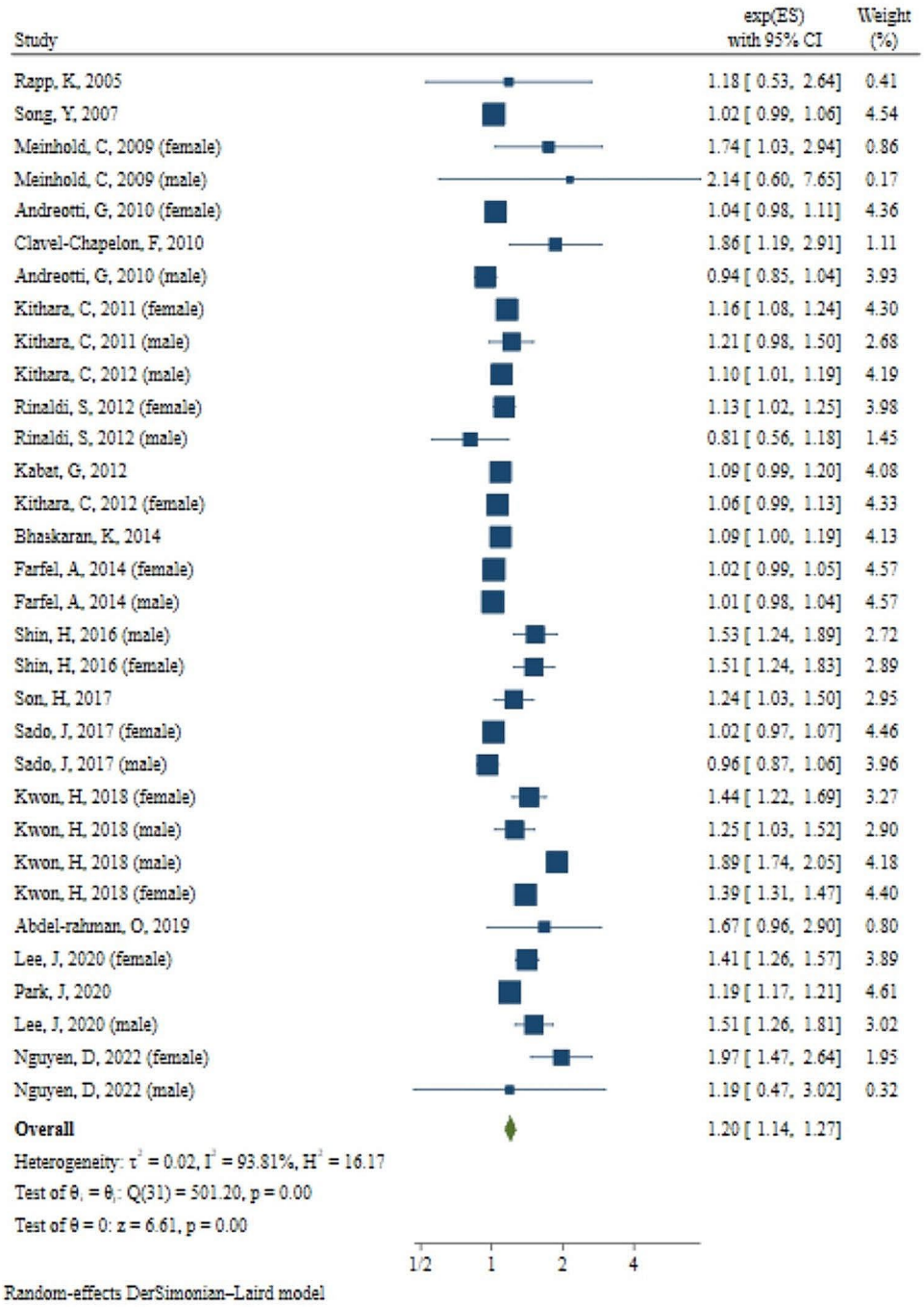

Fig. 4 Effect estimate (HR) of the association between indicators of adiposity and the risk of thyroid cancer

By comparison, Ma et al. [44] reported a more pronounced correlation among women who were obese (RR = 1.43, 95% CI = 1.25–1.64) compared to men who were obese (RR = 1.26, 95% CI = 1.13–1.40). In contrast, a meta-analysis conducted by Dobbins et al. [45] yielded contrasting results, revealing no link between obesity and thyroid cancer among both men (RR = 1.12, 95% CI = 0.72–1.72) and women (RR = 1.03, 95% CI = 0.87–1.23). We are aware of the previous reviews concerning obesity and thyroid cancer [46–49]. However, those publications did not quantitatively summarize the documents on the association between adiposity and risk of TC [46–49]. The global observation of higher thyroid cancer incidence among females [50–52] indicates the significant influence of hormones and reproductive factors in the development of TC.

From a biological perspective, the connection between heightened adiposity and the risk of thyroid cancer can be ascribed to various mechanisms proposed in both experimental and epidemiological investigations. Adiposity is linked to insulin resistance [53], which presents a potential

Table 2 Subgroup estimates of studies reporting OR/RR for the association between adiposity indicators and risk of thyroid cancer stratified by some study characteristics

Study characteristics	Subgroups	N	OR/RR (95%CI)	P	I^2	P heterogeneity between subgroups
Age	< 50 years	6	1.02 (1.01, 1.03)	< 0.001	0.00	0.09
	≥ 50 years	4	1.18 (1.03, 1.36)	0.01	98.00	
	Not reported	1	1.12 (0.70, 1.78)	0.63	--	
Sex	Male	5	1.10 (0.91, 1.34)	0.30	96.64	0.95
	Female	3	1.09 (0.99, 1.21)	0.07	97.27	
	Both sexes	3	1.13 (0.93, 1.37)	0.21	69.39	
Obesity index	BMI or weight	9	1.02 (1.00, 1.04)	< 0.01	26.14	0.01
	WC	2	1.24 (1.06, 1.44)	< 0.01	97.38	
Region	Europe	5	1.02 (1.01, 1.03)	< 0.001	0.00	0.02
	Aisa	4	1.21 (1.07, 1.38)	< 0.01	92.18	
	America	2	1.15 (0.83, 1.59)	0.38	81.70	

Abbreviations BMI, body mass index; WC, waist circumference

Table 3 Subgroup estimates of studies reporting HR for the association between adiposity indicators and risk of thyroid cancer stratified by some study characteristics

Study characteristics	Subgroups	N	HR (95%CI)	P	I^2	P heterogeneity between subgroups
Age	< 50 years	10	1.31 (1.17, 1.46)	< 0.001	97.16	0.09
	≥ 50 years	15	1.13 (1.05, 1.22)	< 0.01	88.82	
	Not reported	7	1.19 (1.04, 1.35)	< 0.01	87.02	
Sex	Male	12	1.20 (1.02, 1.41)	0.02	95.42	0.86
	Female	15	1.19 (1.11, 1.28)	< 0.001	92.29	
	Both sexes	5	1.17 (1.10, 1.23)	< 0.001	26.56	
Obesity index	BMI or weight	29	1.22 (1.14, 1.30)	< 0.001	93.42	0.11
	WC	3	1.12 (1.03, 1.21)	< 0.01	85.62	
Region	Europe	5	1.11 (0.98, 1.27)	0.08	51.07	< 0.01
	Aisa	17	1.26 (1.17, 1.36)	< 0.001	96.56	
	America	10	1.08 (1.02, 1.14)	< 0.01	55.97	

Abbreviations BMI, body mass index; WC, waist circumference

Table 4 Meta-regression for the effect of age and follow-up duration

Type of effect measure	Potential confounder	No. of effect size	Coefficient	SE	P-value	I^2
Studies reporting OR/RR	Age	10	0.009	0.006	0.12	95.67
	Follow-up duration	11	-0.006	0.004	0.18	94.92
Studies reporting HR	Age	25	-0.002	0.003	0.48	94.56
	Follow-up duration	29	-0.007	0.001	< 0.001	83.35

Abbreviations SE, standard error

risk factor for thyroid cancer [54]. However, research exploring the connection between insulin resistance and thyroid cancer is limited, and the results are still subject to debate [55–57]. Chronic inflammation triggered by the secretion of adipokines from adipose tissue [58], oxidative stress [59], and the nuclear factor κB system [60] are associated with cancer progression and could potentially play a role in thyroid-specific carcinogenesis as well. As an illustration, a recent study demonstrated that inducing obesity through diet in mice led to elevated leptin levels, which were correlated with increased TC [61]. Furthermore, adipose tissue generates adiponectin, an adipokine endowed with anti-inflammatory and anti-proliferative properties. The diminished levels of adiponectin observed in obesity could potentially undermine its protective influence against cancer initiation. Insulin resistance, frequently linked to obesity, contributes to heightened levels of insulin and insulin-like growth factor-1 (IGF-1). These hormones exert mitogenic and anti-apoptotic effects, thereby enhancing cell proliferation and survival. Their disruption in the context of obesity could potentially play a role in triggering cellular alterations that drive thyroid carcinogenesis [49]. A growing body of epidemiological evidence indicates a positive correlation between obesity and thyroid-stimulating hormone (TSH) levels in individuals with normal thyroid function (euthyroid) [62, 63]. TSH is implicated in the mitogenic pathways of the thyroid gland [64], and elevated TSH levels have been associated with an elevated risk of TC [65].

A significant advantage of our study lies in its extensive scope as the most comprehensive meta-analysis to incorporate weight, waist and hip circumferences, and waist-to-hip ratio.

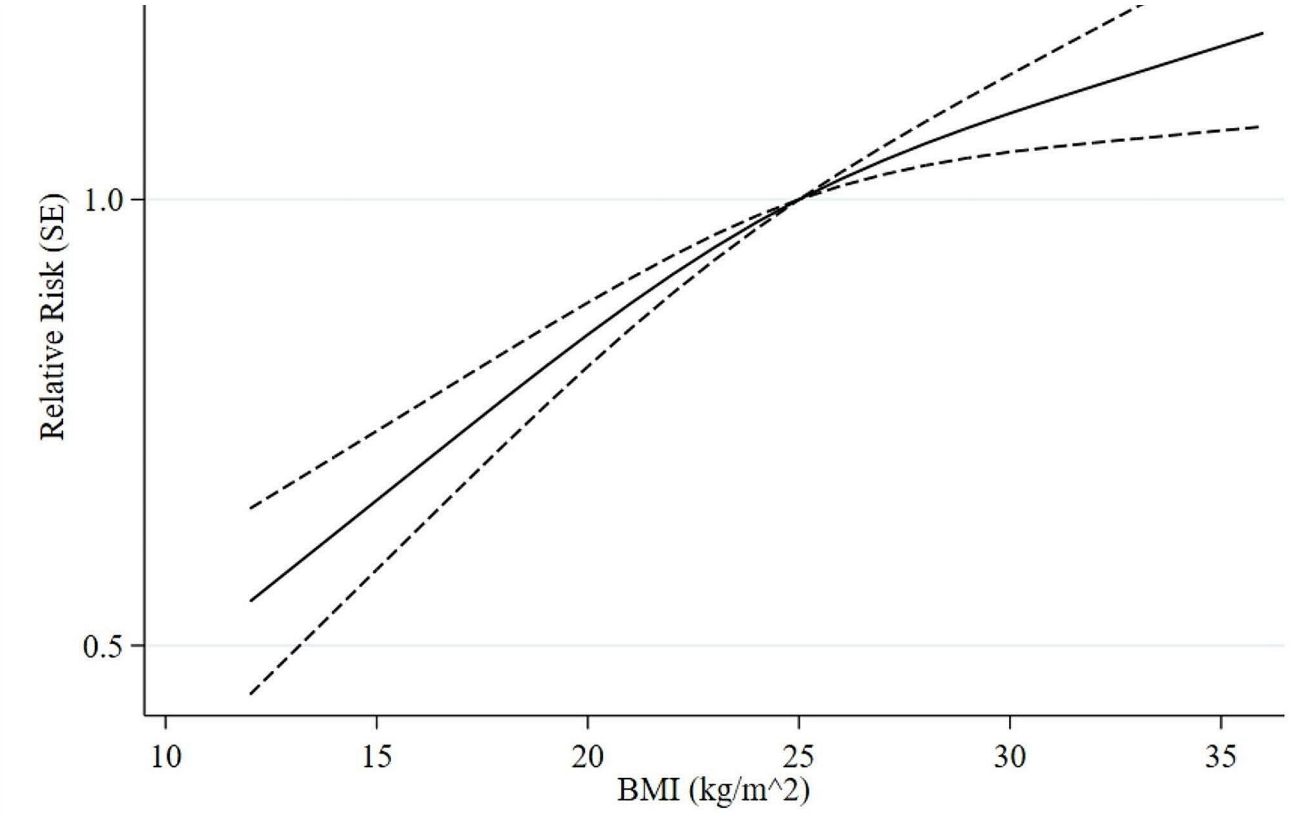

Fig. 5 Dose–response association between BMI and thyroid cancer risk

Another notable asset of our study is its substantial sample size, enhancing the robustness of the findings against the potential impacts of any individual study.

However, when comparing our study to others, it's crucial to recognize certain limitations. Firstly, it's important to note that the studies incorporated into our meta-analysis exhibited differences in their designs, populations, and approaches to assessing adiposity. This heterogeneity could introduce variability in the calculated effect estimates, underscoring the need to consider this aspect when interpreting the results. Secondly, despite attempts to account for potential confounders, complete exclusion of residual confounding remains uncertain. Furthermore, although Begg's test suggests a low likelihood of publication bias, its potential influence on the overall findings cannot be disregarded entirely.

Conclusion

In conclusion, our meta-analysis contributes additional evidence that reinforces the link between indicators of adiposity and the risk of thyroid cancer. The findings are consistent with previous research and highlight the need for continued efforts in understanding the complex interplay between obesity, adipose tissue-derived factors, and thyroid cancer development. Further investigation into the specific molecular pathways and signaling cascades mediating this relationship is warranted. Targeted interventions aimed at reducing obesity-related risk factors could have significant implications for thyroid cancer prevention and management.

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Author contributions B.A., M.H. and M.V. conceived and designed the study. B.A. and F.A. conducted the systematic search, screened articles, and read the full texts for eligibility. F.A., B.A., A.R.A, and A.V. extracted data from the original studies and evaluated the studies for risk of bias. B.A., A.V. and A.R.A contributed to the interpretation of the results and wrote the first draft of the manuscript. M.H., and M.V. critically revised the manuscript. All authors have read and approved the final manuscript.

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Declarations

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References

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Pineros M, Znaor A, Bray F. 2019 estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 1953;144:1941.
2. James BC, Mitchell JM, Jeon HD, Vasilottos N, Grogan RH, Aschebrook-Kilfoy B. An update in international trends in incidence rates of thyroid cancer, 1973–2007. Cancer Causes Control. 2018;29:465–73.
3. Vaccarella S, Franceschi S, Bray F, Wild CP, Plummer M, Dal Maso. L 2016 Worldwide thyroid-cancer epidemic? The increasing impact of overdiagnosis. N Engl J Med 375: 614–7.
4. Flegal KM. Epidemiologic aspects of overweight and obesity in the United States. Physiol Behav. 2005;86:599–602.
5. Budny A, Grochowski C, Kozlowski P, et al. Obesity as a tumour development triggering factor. Ann Agric Environ Med. 2019;26:13–23.
6. Arnold M, Pandeya N, Byrnes G, et al. Global burden of cancer attributable to high body-mass index in 2012: a population-based study. Lancet Oncol. 2015;16:36–46.
7. Matrone A, Ferrari F, Santini F, Elisei R. Obesity as a risk factor for thyroid cancer. Curr Opin Endocrinol Diabetes Obes. October 2020;27(5):358–63. https://doi.org/10.1097/MED.0000000000000556.
8. Matrone A, Ceccarini G, Beghini M, Ferrari F, Gambale C, D'Aqui M, et al. Potential impact of BMI on the aggressiveness of presentation and clinical outcome of differentiated thyroid Cancer. J Clin Endocrinol Metab. 2020;105(4):e1124–34. https://doi.org/10.1210/clinem/dgz312.
9. Kitahara CM, Pfeiffer RM, Sosa JA, Shiels MS. Impact of overweight and obesity on US papillary thyroid Cancer Incidence trends (1995–2015). J Natl Cancer Inst. 2020;112(8):810–7. https://doi.org/10.1093/jnci/djz202.
10. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev. 2021;10(1):89.
11. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M et al. December. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute. Accessed at www.ohri.ca/programs/clinical_epidemiology/oxford.asp on 2 2012.
12. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25:603e5.
13. Park JH, Cho HS, Yoon JH. Thyroid Cancer in patients with metabolic syndrome or its components: a Nationwide Population-based Cohort Study. Cancers (Basel). 2022;14(17):4106. https://doi.org/10.3390/cancers14174106. PMID: 36077642; PMCID: PMC9454651.
14. Dung N, Nguyen JH, Kim MK. Association of Metabolic Health and Central Obesity with the risk of thyroid Cancer: data from the Korean Genome and Epidemiology Study. Cancer Epidemiol Biomarkers Prev. March 2022;1(3):543–53. https://doi.org/10.1158/1055-9965.EPI-21-0255.
15. Ahmadi S, Pappa T, Kang AS, Coleman AK, Landa I, Marqusee E, Kim M, Angell TE, Alexander EK. Point of Care Measurement of Body Mass Index and thyroid nodule Malignancy Risk Assessment. Front Endocrinol (Lausanne). 2022;13:824226. https://doi.org/10.3389/fendo.2022.824226. PMID: 35222281; PMCID: PMC8873520.
16. Lee JH, Youn S, Jung S, Kim K, Chai YJ, Chung YS, Park WS, Lee KE, Yi KH. A national database analysis for factors associated with thyroid cancer occurrence. Sci Rep. 2020;10(1):17791. https://doi.org/10.1038/s41598-020-74546-3. PMID: 33082385; PMCID: PMC7576121.
17. Park JH, Choi M, Kim JH, Kim J, Han K, Kim B, Kim DH, Park YG. Metabolic syndrome and the risk of thyroid Cancer: a Nationwide Population-based Cohort Study. Thyroid. 2020;30(10):1496–504. Epub 2020 Jul 15. PMID: 32524894.
18. Abdel-Rahman O. Prediagnostic BMI and thyroid cancer incidence in the PLCO trial. Future Oncol. 2019;15(30):3451–3456. https://doi.org/10.2217/fon-2019-0292. PMID: 31646903.
19. Kwon H, Han KD, Park CY. Weight change is significantly associated with risk of thyroid cancer: a nationwide population-based cohort study. Sci Rep. 2019;9(1):1546. https://doi.org/10.1038/s41598-018-38203-0. PMID: 30733504; PMCID: PMC6367378.
20. Sado J, Kitamura T, Sobue T, Sawada N, Iwasaki M, Sasazuki S, Yamaji T, Shimazu T, Tsugane S, JPHC Study Group. Risk of thyroid cancer in relation to height, weight, and body mass index in Japanese individuals: a population-based cohort study. Cancer Med. 2018;7(5):2200–10. Epub 2018 Mar 25. PMID: 29577664; PMCID: PMC5943544.
21. Al-Ammar Y, Al-Mansour B, Al-Rashood O, Tunio MA, Islam T, Al-Asiri M, Al-Qahtani KH. Impact of body mass index on survival outcome in patients with differentiated thyroid cancer. Braz J Otorhinolaryngol. 2018 Mar-Apr;84(2):220–6. Epub 2017 Feb 28. PMID: 28325623; PMCID: PMC9449218.
22. Son H, Lee H, Kang K, Lee I. The risk of thyroid cancer and obesity: a nationwide population-based study using the Korea National Health Insurance Corporation cohort database. Surg Oncol. 2018;27(2):166–71. Epub 2018 Mar 16. PMID: 29937167.
23. Shin HY, Jee YH, Cho ER. Body mass index and incidence of thyroid cancer in Korea: the Korean Cancer Prevention Study-II. J Cancer Res Clin Oncol. 2017;143(1):143–9. Epub 2016 Sep 23. PMID: 27662845.
24. Farfel A, Kark JD, Derazne E, Tzur D, Barchana M, Lazar L, Afek A, Shamiss A. Predictors for thyroid carcinoma in Israel: a national cohort of 1,624,310 adolescents followed for up to 40 years. Thyroid. 2014;24(6):987–93. Epub 2014 Mar 17. PMID: 24483833.
25. Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults. Lancet. 2014;384(9945):755–65. https://doi.org/10.1016/S0140-6736(14)60892-8. Epub 2014 Aug 13. PMID: 25129328; PMCID: PMC4151483.
26. Kitahara CM, Platz EA, Park Y, Hollenbeck AR, Schatzkin A, Berrington de González A. Body fat distribution, weight change during adulthood, and thyroid cancer risk in the NIH-AARP Diet and Health Study. Int J Cancer. 2012;130(6):1411–9. https://doi.org/10.1002/ijc.26161. Epub 2011 Aug 2. PMID: 21544808; PMCID: PMC3242922.
27. Kabat GC, Kim MY, Thomson CA, Luo J, Wactawski-Wende J, Rohan TE. Anthropometric factors and physical activity and risk of thyroid cancer in postmenopausal women. Cancer Causes Control. 2012;23(3):421–30. https://doi.org/10.1007/s10552-011-9890-9. Epub 2012 Jan 3. PMID: 22212611.

28. Rinaldi S, Lise M, Clavel-Chapelon F, Boutron-Ruault MC, Guillas G, Overvad K, Tjønneland A, Halkjær J, Lukanova A, Kaaks R, Bergmann MM, Boeing H, Trichopoulou A, Zylis D, Valanou E, Palli D, Agnoli C, Tumino R, Polidoro S, Mattiello A, Bueno-de-Mesquita HB, Peeters PH, Weiderpass E, Lund E, Skeie G, Rodríguez L, Travier N, Sánchez MJ, Amiano P, Huerta JM, Ardanaz E, Rasmuson T, Hallmans G, Almquist M, Manjer J, Tsilidis KK, Allen NE, Khaw KT, Wareham N, Byrnes G, Romieu I, Riboli E, Franceschi S. Body size and risk of differentiated thyroid carcinomas: findings from the EPIC study. Int J Cancer. 2012;131(6):E1004–14. https://doi.org/10.1002/ijc.27601. Epub 2012 May 14. PMID: 22511178.
29. Almquist M, Johansen D, Björge T, Ulmer H, Lindkvist B, Stocks T, Hallmans G, Engeland A, Rapp K, Jonsson H, Selmer R, Diem G, Häggström C, Tretli S, Stattin P, Manjer J. Metabolic factors and risk of thyroid cancer in the metabolic syndrome and Cancer project (Me-Can). Cancer Causes Control. 2011;22(5):743–51. https://doi.org/10.1007/s10552-011-9747-2. Epub 2011 Mar 6. PMID: 21380729.
30. Kitahara CM, Platz EA, Freeman LE, Hsing AW, Linet MS, Park Y, Schairer C, Schatzkin A, Shikany JM, Berrington de González A. Obesity and thyroid cancer risk among U.S. men and women: a pooled analysis of five prospective studies. Cancer Epidemiol Biomarkers Prev. 2011;20(3):464–72. https://doi.org/10.1158/1055-9965.EPI-10-1220. Epub 2011 Jan 25. PMID: 21266520; PMCID: PMC3079276.
31. Andreotti G, Hou L, Beane Freeman LE, Mahajan R, Koutros S, Coble J, Lubin J, Blair A, Hoppin JA, Alavanja M. Body mass index, agricultural pesticide use, and cancer incidence in the Agricultural Health Study cohort. Cancer Causes Control. 2010;21(11):1759–75. https://doi.org/10.1007/s10552-010-9603-9. Epub 2010 Aug 22. PMID: 20730623; PMCID: PMC2962760.
32. Clavel-Chapelon F, Guillas G, Tondeur L, Kernaleguen C, Boutron-Ruault MC. Risk of differentiated thyroid cancer in relation to adult weight, height and body shape over life: the French E3N cohort. Int J Cancer. 2010;126(12):2984-90. https://doi.org/10.1002/ijc.25066. PMID: 19950225.
33. Leitzmann MF, Brenner A, Moore SC, Koebnick C, Park Y, Hollenbeck A, Schatzkin A, Ron E. Prospective study of body mass index, physical activity and thyroid cancer. Int J Cancer. 2010;126(12):2947–56. https://doi.org/10.1002/ijc.24913. PMID: 19795465; PMCID: PMC2919690.
34. Meinhold CL, Ron E, Schonfeld SJ, Alexander BH, Freedman DM, Linet MS, Berrington de González A. Nonradiation risk factors for thyroid cancer in the US Radiologic technologists Study. Am J Epidemiol. 2010;171(2):242–52. https://doi.org/10.1093/aje/kwp354. Epub 2009 Nov 30. PMID: 19951937; PMCID: PMC3290908.
35. Song YM, Sung J, Ha M. Obesity and risk of cancer in postmenopausal Korean women. J Clin Oncol. 2008;26(20):3395–402. https://doi.org/10.1200/JCO.2007.15.7867. PMID: 18612154.
36. Engeland A, Tretli S, Akslen LA, Bjørge T. Body size and thyroid cancer in two million Norwegian men and women. Br J Cancer. 2006;95(3):366–70. https://doi.org/10.1038/sj.bjc.6603249. Epub 2006 Jul 11. PMID: 16832414; PMCID: PMC2360634.
37. Samanic C, Chow WH, Gridley G, Jarvholm B, Fraumeni JF Jr. Relation of body mass index to cancer risk in 362,552 Swedish men. Cancer Causes Control. 2006;17(7):901-9. https://doi.org/10.1007/s10552-006-0023-9. PMID: 16841257.
38. Rapp K, Schroeder J, Klenk J, Stoehr S, Ulmer H, Concin H, Diem G, Oberaigner W, Weiland SK. Obesity and incidence of cancer: a large cohort study of over 145,000 adults in Austria. Br J Cancer. 2005;93(9):1062–7. https://doi.org/10.1038/sj.bjc.6602819. PMID: 16234822; PMCID: PMC2361672.
39. Oh SW, Yoon YS, Shin SA. Effects of excess weight on cancer incidences depending on cancer sites and histologic findings among men: Korea National Health Insurance Corporation Study. J Clin Oncol. 2005;23(21):4742-54.https://doi.org/10.1200/JCO.2005.11.726. PMID: 16034050.
40. Son H, Lee H, Kang K, Lee I. The risk of thyroid cancer and obesity: a nationwide population-based study using the Korea National Health Insurance Corporation cohort database. Surg Oncol. 2018;27:166–71.
41. Matrone A, Ferrari F, Santini F, Elisei R. October. Obesity as a risk factor for thyroid cancer. Current Opinion in Endocrinology & Diabetes and Obesity 27(5):p 358–363, 2020.| https://doi.org/10.1097/MED.0000000000000556.
42. Kwon H, Chang Y, Cho A, et al. Metabolic obesity phenotypes and thyroid cancer risk: a cohort study. Thyroid. 2019;29:349–58.
43. Kitahara CM, Pfeiffer RM, Sosa JA, Shiels MS. Impact of overweight and obesity on U.S. papillary thyroid cancer incidence trends (1995–2015). J Natl Cancer Inst 2019. [Online ahead of print].
44. Ma J, Huang M, Wang L, Ye W, Tong Y, Wang H. Obesity and risk of thyroid cancer: evidence from a meta-analysis of 21 observational studies. Med Sci Monit. 2015;21:283–91.
45. Dobbins M, Decorby K, Choi BC. The association between obesity and cancer risk: a meta-analysis of observational studies from 1985 to 2011. ISRN Prev Med. 2013;1–16. 10.5402/2013/680536.
46. Peterson E, De P, Nuttall R. BMI, diet and female reproductive factors as risks for thyroid cancer: a systematic review. PLoS ONE. 2012;7:e29177.
47. Pappa T, Alevizaki M. Obesity and thyroid cancer: a clinical update. Thyroid. 2014;24:190–9.
48. Marcello MA, Cunha LL, Batista FA, Ward LS. Obesity and thyroid cancer. Endocr Relat Cancer. 2014;21:T255–71.
49. Pazaitou-Panayiotou K, Polyzos SA, Mantzoros CS. Obesity and thyroid cancer: epidemiologic associations and underlying mechanisms. Obes Rev. 2013;14:1006–22.
50. Kilfoy BA, Zheng T, Holford TR, Han X, Ward MH, Sjodin A, Zhang Y, Bai Y, Zhu C, Guo GL, Rothman N, Zhang Y. 2009 International patterns and trends in thyroid cancer incidence, 1973–2002. Cancer Causes Control 20: 525–31.
51. Hong S, Won YJ, Lee JJ, Jung KW, Kong HJ, Im JS, Seo HG. Community of Population-based Regional Cancer R 2021 Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2018. Cancer Res Treat 53: 301–15.
52. Li M, Pei J, Xu M, Shu T, Qin C, Hu M, Zhang Y, Jiang M, Zhu C. Changing incidence and projections of thyroid cancer in mainland China, 1983–2032: evidence from Cancer incidence in five continents. Cancer Causes Control. 2021;32:1095–105.
53. Jung UJ, Choi MS. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. Int J Mol Sci. 2014;15:6184–223.
54. Gursoy A. Rising thyroid cancer incidence in the world might be related to insulin resistance. Med Hypotheses. 2010;74:35–6.
55. Balkan F, Onal ED, Usluogullari A, et al. Is there any association between insulin resistance and thyroid cancer? A case control study. Endocrine. 2014;45:55–60.
56. Bae MJ, Kim SS, Kim WJ, et al. High prevalence of papillary thyroid cancer in Korean women with insulin resistance. Head Neck. 2014. https://doi.org/10.1002/hed.23848.
57. Akker M, Guldiken S, Sipahi T, et al. Investigation of insulin resistance gene polymorphisms in patients with differentiated thyroid cancer. Mol Biol Rep. 2014;41:3541–7.
58. Park J, Scherer PE. Leptin and cancer: from cancer stem cells to metastasis. Endocr Relat Cancer. 2011;18:C25–9.
59. Metere A, Chiesa C, Di Cosimo C, Fierro G, Giacomelli L, Pietraforte D. A novel approach to study oxidative stress in

thyroid diseases: a preliminary study. Eur Rev Med Pharmacol Sci. 2012;16:646–52.
60. Pacifico F, Leonardi A. Role of NF-kappaB in thyroid cancer. Mol Cell Endocrinol. 2010;321:29–35.
61. Kim WG, Park JW, Willingham MC, Cheng SY. Diet-induced obesity increases tumor growth and promotes anaplastic change in thyroid cancer in a mouse model. Endocrinology. 2013;154:2936–47.
62. Roef G, Lapauw B, Goemaere S, et al. Body composition and metabolic parameters are associated with variation in thyroid hormone levels among euthyroid young men. Eur J Endocrinol. 2012;167:719–26.
63. Alevizaki M, Saltiki K, Voidonikola P, Mantzou E, Papamichael C, Stamatelopoulos K. Free thyroxine is an independent predictor of subcutaneous fat in euthyroid individuals. Eur J Endocrinol. 2009;161:459–65.
64. Parameswaran R, Brooks S, Sadler GP. Molecular pathogenesis of follicular cell derived thyroid cancers. Int J Surg. 2010;8:186–93.
65. Haymart MR, Glinberg SL, Liu J, Sippel RS, Jaume JC, Chen H. Higher serum TSH in thyroid cancer patients occurs independent of age and correlates with extrathyroidal extension. Clin Endocrinol (Oxf). 2009;71:434–9.