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Association between depressive symptoms and thyroid nodule incidence in women: a prospective observational study

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Abstract

Background This study aimed to investigate the association between depressive symptoms and the incidence of thyroid nodules (TNs) in Chinese adults, and explore whether the development, persistence, or recovery from depressive symptoms influences the risk of developing TNs.

Methods A total of 1,537 Chinese adults who underwent medical check-ups, including blood tests, Zung Self-Rating Depression Scales (SDS), and thyroid ultrasound examinations, were included. The association between depressive symptoms and TN prevalence was evaluated, and 818 participants free of TNs at baseline were followed over time. TN incidence rates were analyzed across different mental health statuses: depression-free, depression-developed, depression-recovered, and depression-persistent.

Results The prevalence of depressive symptoms was 31.95%, significantly higher in women than in men (42.60% vs. 25.82%). The prevalence of TNs was also higher in women (38.68% vs. 21.52%). Among women, participants with depressive symptoms had shorter height, higher levels of fasting plasma glucose (FPG), triglycerides (TG), and glutamyl transpeptidase (GGT), lower high-density lipoprotein cholesterol (HDL-C), and a significantly higher prevalence of TNs (46.44% vs. 32.92%, $p < 0.01$) compared to those without depressive symptoms. Although the FPG levels in depressive women were significantly higher than in non-depressive women, the levels of FPG in both groups remained within the clinically normal range. These differences were not observed in men. Over a mean follow-up of 2.75 years in women, the depression-persistent group (16.48/100 person-years) had a significantly higher TN incidence compared to the depression-free (6.43/100 person-years; age-adjusted HR: 2.679, 95% CI: 1.513–4.742, $p = 0.001$).

Conclusions Women with persistent depressive symptoms had a higher risk of developing TNs, suggesting that mental health status may influence TN development in women.

Keywords Chinese adults, Depressive symptoms, Prospective study, Thyroid nodules, Women's health

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Background

Thyroid nodules (TNs) are increasingly recognized as a common thyroid disorder, with a global prevalence that is detected via ultrasound in 20–67% of individuals [1]. The rise in high-resolution ultrasonography is one of the key factors contributing to this increasing trend [2]. Intrinsic factors, such as gender, age, race, family history, and metabolic disorders, are also associated with the prevalence of TNs [3–5]. TNs can present in various forms, including benign, malignant, hormonally active, or inactive, and can be symptomatic or asymptomatic [6]. This variability has significant clinical implications, as while benign TNs often require minimal intervention, malignant or hormonally active nodules may necessitate more intensive management. At present, the relationship between mental health disorders and TNs has received limited attention [7].

Depression, a prevalent mental disorder with a lifetime prevalence of 8–12%, poses a significant public health challenge worldwide [8]. It is associated with a variety of health conditions, including obesity [9], diabetes [10], cardiovascular disease [11], osteoporosis [12], immune disorders [13], and cancers [14]. Currently, the bidirectional effects of thyroid dysfunction and mental health, including emotional and cognitive abilities, are well-established. Both excess and deficient levels of thyroid hormone can lead to mood disorders, including depression, which are often treatable with appropriate management of thyroid imbalances. According to Boswell, 50% of patients with hypothyroidism experience symptoms of depression [15]. Conversely, overt hypothyroidism is present in 1–4% of patients with affective disorders, while subclinical hypothyroidism affects 4–40% of these individuals [16]. Another study focused on the diurnal change of TSH concentration and found that the nocturnal increase in TSH concentration correlated negatively with the severity of clinical depression symptoms [17]. The mendelian randomization study performed by Su et al. revealed the positive bidirectional association between depression and autoimmune thyroiditis risk, however, the underlying biological mechanism requires further investigation [18].

Despite these insights, research on the impact of mental health disorders and the specific relationship between depression and TNs remains limited. The Self-Rating Depression Scale (SDS) is a widely used metric for assessing depressive symptoms, providing valuable insights into the severity and dynamics of depression. Incorporating this scale in our study enhances our understanding of how depressive symptoms relate to TN incidence. Additionally, while depression significantly affects thyroid function, emerging evidence indicates that other lifestyle and environmental factors, such as dietary habits, stress levels, and overall lifestyle, may also be important determinants of thyroid health.

Therefore, this study aims to investigate the association between depressive symptoms and the incidence of TNs. Additionally, given the dynamic nature of mental health, we examined whether the onset, persistence, or recovery from depressive symptoms is associated with variations in TN risk.

Methods

Study design and population

The prospective observational study was conducted from January 1st, 2013 to December 31st, 2021, with continuous data collection throughout this period. Chinese adults aged 18–65 years who underwent routine health check-ups were recruited at the Health Management Center of Foshan Hospital of Traditional Chinese Medicine. These check-ups included blood tests, SDS assessments, and thyroid ultrasound examinations. Participants were excluded if they had any of the following conditions: (a) a history of diagnosed depression or other mental or neurological disorders, or previous treatment with psychotherapy or medication; (b) a history of thyroid diseases such as hyperthyroidism, hypothyroidism, subacute thyroiditis, or Hashimoto's thyroiditis; (c) a history of thyroid treatments, including medication, surgery, or head and neck radiotherapy; (d) a history of cancer; (e) pregnancy or lactation. Participants were not censored, and follow-up continued until TNs were detected via ultrasound or until December 31st, 2021.

The study protocol was approved by the Human Research Committee of Foshan Hospital of Traditional Chinese Medicine, and all participants provided written informed consent. This study was conducted in compliance with the ethical standards of the Declaration of Helsinki.

Grouping and follow-up

TNs were defined as distinct lesions within the thyroid gland that were radiologically distinguishable from the surrounding thyroid parenchyma and could present as solid, spongiform, cystic, or mixed nodules [19]. Depressive symptoms were assessed using the SDS method. An SDS index score above 49 (raw score above 40) indicates clinically significant symptoms [20]. Participants with SDS index scores greater than 49 were classified as having depressive symptoms [21]. At baseline, participants were divided into two groups: the depressive symptoms group and the control group.

Participants were followed up annually, receiving text message reminders to return to the hospital for medical check-ups, along with psychological and lifestyle counseling. During these follow-up visits, individuals with psychological or metabolic abnormalities received

appropriate treatment. Follow-up continued until TNs were detected via ultrasound during a medical examination, or until December 31st, 2021.

Participants were classified based on their SDS scores at baseline and during follow-up. The most recent follow-up SDS score was used for classification: (1) Depression-free: Participants consistently free from depressive symptoms throughout the study (SDS ≤ 49 at all time points); (2) Depression-developed: Participants who developed new depressive symptoms (SDS ≤ 49 at baseline but > 49 after follow-up); (3) Depression-recovery: Participants who recovered from pre-existing depressive symptoms (SDS > 49 at baseline but ≤ 49 after follow-up); (4) Depression-persistent: Participants who consistently experienced depressive symptoms (SDS > 49 throughout the study).

Data collection and definition

All participants had their height and weight measured while wearing loose clothing and standing barefoot. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). After 10 min of rest, blood pressure was measured three times on the right arm using appropriately sized cuffs, and the average of the three readings was used for analysis.

Fasting blood samples were collected at baseline and the end of follow-up. FPG was measured using the hexokinase/G-6-PDH method. TG and total cholesterol (TC) were assessed by the peroxidase-chromogen method using glycerol-3-phosphate kinase and cholesterol esterase-cholesterol oxidase, respectively. Low-density lipoprotein cholesterol (LDL-C) and HDL-C were measured using a direct one-step method. Uric acid (UA) was assessed using the uricase method. Alanine transaminase (ALT), aspartate aminotransferase (AST), and GGT levels were measured using a rating method, while creatinine (Cr) was measured via the sarcosine oxidase method. Free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH) levels were determined using a chemiluminescence assay (Sangon Biotech, Shanghai).

Ultrasound examinations of TNs were conducted by senior sonographers with over 10 years of experience, using a B-mode high-resolution tomographic ultrasound system (Esaote, Genova, Italy). The participants were positioned supine with their necks extended, supported by a positioning pillow.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD), while categorical variables are expressed as numbers (percentages). Differences between the depressive symptoms group and the control group at baseline were analyzed using independent t-tests for continuous variables and Pearson's chi-square tests for categorical variables. To compare the depression-free, depression-developed, depression-recovery, and depression-persistent groups, analysis of variance (ANOVA), LSD post-hoc tests, and Pearson's chi-square tests were employed.

Multivariable logistic regression analysis was performed to identify potential risk factors associated with the prevalence of TNs at baseline in the total sample as well as in the male and female subgroups. The stepwise regression model included the following covariates: age, gender, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), FPG, TG, TC, LDL-C, HDL-C, UA, ALT, AST, GGT, Cr, FT3, FT4, TSH, and SDS score. Cox proportional hazard models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the development of TNs during the follow-up period [22].

All statistical analyses were conducted using SPSS version 25 (IBM Corp., Armonk, NY, USA). For multiple comparisons, a Bonferroni correction was applied, given that there were six comparisons, resulting in a corrected significance threshold of 0.05/6 = 0.0083. P value < 0.05 or the Bonferroni corrected P value < 0.0083 was considered statistically significant.

Results

Baseline characteristics and risk factors for TN prevalence

A total of 1,537 participants (mean age 36.07 ± 8.27 years) were included in the baseline analysis(Fig. 1), comprising 976 men (mean age 35.98 ± 8.21 years) and 561 women (mean age 36.23 ± 8.36 years). The prevalence of depressive symptoms was 31.95%, with a significantly higher rate in women compared to men (42.60% vs. 25.82%, $p < 0.01$). The overall prevalence of TNs was 27.78%, which was also significantly higher in women than in men (38.68% vs. 21.52%, $p < 0.01$).

In both men and women, participants with depressive symptoms were older than those without (Table 1). Among women, participants with depressive symptoms had shorter height, higher levels of FPG, TG, and GGT, lower HDL-C, and a significantly higher prevalence of TNs (46.44% vs. 32.92%, $p < 0.01$) compared to those without depressive symptoms. These differences were not observed in men.

Multivariate logistic regression analysis revealed that gender and age were independent risk factors across the entire cohort (Table 2). In men, age was the only independent risk factor for TNs, whereas in women, age, ALT, and the SDS score were independent predictors of TNs.

Characteristics of participants in the follow-up study

Out of the initial cohort, 1,110 participants were TN-free at baseline. 201 participants declined follow-up

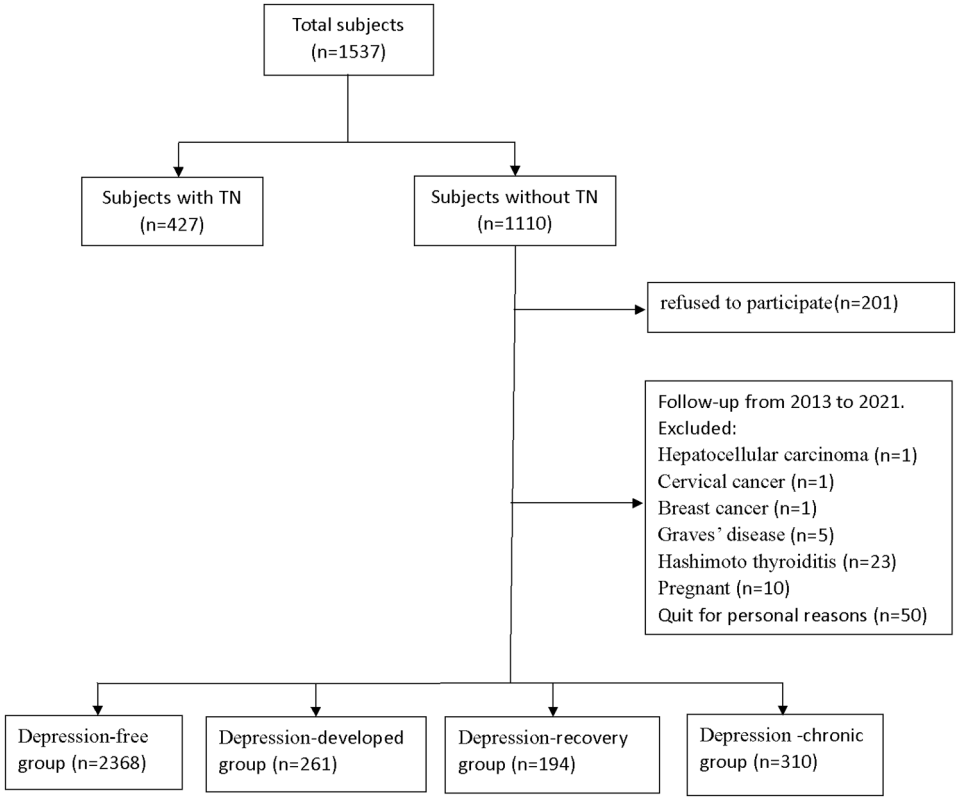

Fig. 1 Flowchart of study population

participation, leaving 909 participants who entered the follow-up study. During follow-up, there were instances of cancer diagnoses, new thyroid diseases, pregnancy, and personal withdrawals, resulting in 818 participants (571 men and 247 women) completing an average follow-up period of 2.75 years. Table 3 presents baseline and follow-up data on depressive symptoms for these 818 participants. Among men, those in the Depression-developed and Depression-persistent groups tended to be older, while the Depression-free and Depression-recovery groups included younger individuals. Similarly, among women, the Depression-persistent group consisted of the oldest participants. As expected, participants in the Depression-persistent and Depression-developed groups were older at baseline, indicating the well-established relationship between age and increased prevalence of depressive symptoms.

During follow-up, men in the Depression-developed and Depression-persistent groups were older compared to those in the Depression-free and Depression-recovery groups. Additionally, men in the Depression-developed group exhibited higher FPG and GGT levels, along with lower UA levels compared to the Depression-free group. In women, while the Depression-persistent group had older participants and higher FPG levels compared to the Depression-free group, the significant age differences observed at baseline between depressive and non-depressive women were no longer present when comparing depressive subgroups at follow-up. Similarly, no significant differences in height and weight were observed across depressive subgroups at follow-up, suggesting that these baseline characteristics did not persist over time. SDS scores increased from 36.04 ± 6.17 to 52.59 ± 2.85 in the Depression-developed group and decreased from 56.09 ± 4.52 to 43.94 ± 4.23 in the Depression-recovery group, while the SDS scores of the Depression-persistent groups remained at the highest level among the groups in both genders (57.64 ± 5.15 at follow-up in male; 57.00 ± 5.19 at follow-up in female).

Risk of TNs according to changes in depressive symptoms

After adjusting for gender, age and BMI, persistent depressive symptoms were associated with an increased incidence of TNs throughout the follow-up period compared to the Depression-free group (adjusted HR: 1.857, 95% CI: 1.229–2.805, $p = 0.003$) (Table 4). In men, multivariate Cox regression analysis revealed that age was the sole risk factor for TN incidence, with no significant differences in TN incidence among the four depressive symptom groups. However, it is noteworthy that men in this cohort had higher-than-recommended levels of TC and LDL, as well as elevated FPG levels. These elevated markers may contribute to the overall health profile in men, potentially influencing TN development. In women,

Table 1 Baseline characteristics of subjects according to depressive symptoms

	Total ($n=1537$)		*P*	Men ($n=976$)		*P*	Women ($n=561$)		*P*
	Normal	Depressive		Normal	Depressive		Normal	Depressive	
	($n=1046$, 68.05%)	($n=491$, 31.95%)		($n=724$, 74.18%)	($n=252$, 25.82%)		($n=322$, 57.40%)	($n=239$, 42.60%)	
Age (years)	35.28 ± 7.89	37.75 ± 8.79	< 0.001	35.43 ± 7.88	37.55 ± 8.94	0.001	34.94 ± 7.93	37.96 ± 8.64	< 0.001
Height (cm)	166.44 ± 8.11	163.58 ± 8.43	< 0.001	170.03 ± 6.30	169.54 ± 5.92	0.279	158.36 ± 5.47	157.30 ± 5.66	0.024
Weight (kg)	67.96 ± 13.83	64.70 ± 14.18	< 0.001	73.64 ± 11.74	73.25 ± 13.24	0.656	55.17 ± 8.70	55.68 ± 8.35	0.486
BMI (kg/m^2)	24.38 ± 3.84	24.00 ± 3.90	0.073	25.44 ± 3.53	25.42 ± 3.97	0.949	22.02 ± 3.42	22.51 ± 3.20	0.081
SBP (mmHg)	123.25 ± 15.03	121.53 ± 15.59	0.038	127.08 ± 14.18	127.19 ± 14.11	0.915	114.65 ± 13.22	115.56 ± 14.86	0.448
DBP(mmHg)	74.20 ± 10.72	73.22 ± 9.96	0.088	76.31 ± 10.57	76.34 ± 9.97	0.971	69.47 ± 9.49	69.94 ± 8.84	0.546
FPG (mmol/L)	5.28 ± 1.12	5.39 ± 1.30	0.101	5.37 ± 1.26	5.55 ± 1.56	0.100	5.08 ± 0.70	5.21 ± 0.92	0.046
TG (mmol/L)	1.62 ± 1.66	1.59 ± 1.44	0.739	1.88 ± 1.87	1.86 ± 1.43	0.915	1.04 ± 0.78	1.30 ± 1.40	0.005
TC (mmol/L)	5.05 ± 0.95	5.02 ± 1.00	0.630	5.15 ± 0.97	5.26 ± 1.02	0.144	4.82 ± 0.86	4.78 ± 0.92	0.585
LDL-C (mmol/L)	3.00 ± 0.80	2.93 ± 0.85	0.148	3.13 ± 0.80	3.17 ± 0.87	0.562	2.70 ± 0.73	2.69 ± 0.77	0.857
HDL-C (mmol/L)	1.35 ± 0.28	1.38 ± 0.29	0.072	1.27 ± 0.25	1.30 ± 0.28	0.090	1.52 ± 0.28	1.45 ± 0.28	0.004
UA (μmol/L)	383.63 ± 99.17	358.02 ± 103.90	< 0.001	421.42 ± 87.55	416.05 ± 97.52	0.441	298.66 ± 65.48	296.83 ± 69.78	0.751
ALT (U/L)	36.52 ± 63.60	33.75 ± 67.00	0.434	43.57 ± 74.43	45.54 ± 91.17	0.733	20.68 ± 18.08	21.33 ± 12.34	0.641
AST (U/L)	25.89 ± 35.63	25.10 ± 28.09	0.666	28.08 ± 41.66	29.37 ± 38.02	0.665	20.97 ± 13.74	20.60 ± 7.79	0.707
GGT (U/L)	34.80 ± 30.50	32.88 ± 26.15	0.228	42.17 ± 32.88	44.03 ± 30.57	0.433	18.21 ± 13.91	21.11 ± 12.34	0.011
Gr (μmol/L)	68.45 ± 13.04	65.44 ± 14.10	< 0.001	74.27 ± 10.51	74.36 ± 12.35	0.931	55.36 ± 7.51	56.04 ± 8.67	0.325
FT3 (pmol/L)	5.06 ± 0.55	5.07 ± 0.58	0.895	5.15 ± 0.58	5.27 ± 0.60	0.271	4.85 ± 0.42	4.83 ± 0.45	0.822
FT4 (pmol/L)	16.72 ± 2.31	16.47 ± 2.24	0.456	16.97 ± 2.45	16.86 ± 2.54	0.822	16.12 ± 1.81	15.98 ± 1.70	0.749
TSH (mIU/L)	1.73 ± 1.12	1.73 ± 1.08	0.998	1.57 ± 0.91	1.65 ± 1.17	0.662	2.13 ± 1.46	1.83 ± 0.97	0.319
SDS score	36.47 ± 6.86	57.20 ± 5.16	< 0.001	36.32 ± 7.04	56.91 ± 4.85	< 0.001	36.82 ± 6.41	57.49 ± 5.46	< 0.001
TNs, n (%)	253 (24.19)	174 (35.44)	< 0.001	147 (20.30)	63 (25.00)	0.118	106 (32.92)	111 (46.44)	0.001

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; UA, uric acid; ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; Cr, creatinine; FT3, free triiodothyronine; FT4, free tetraiodothyronine; TSH, thyroid stimulating hormone (TSH); SDS, Zung self-rating depression scale; TNs, thyroid nodules

Table 2 Risk factors for TN prevalence among male and female patients

	OR (95%CI)	*P*
Total		
Gender	2,586 (1.765–3.789)	< 0.001
Age	1.037 (1.021–1.053)	< 0.001
Men		
Age	1.033 (1.010–1.056)	0.005
Women		
Age	1.042 (1.016–1.069)	0.001
ALT	1.026 (1.001–1.050)	0.038
SDS score	1.026 (1.007–1.045)	0.008

OR, odds ratio; CI, confidence interval; ALT, alanine transaminase

both age and mental health were identified as risk factors for TNs. When adjusting for age, the incidence rates of TNs were similar among the Depression-free (6.42/100 person-years), Depression-developed (6.71/100 person-years), and Depression-recovery (8.04/100 person-years) groups. However, the Depression-persistent group exhibited a significantly higher incidence of TNs (16.48/100 person-years) compared to the Depression-free group throughout the follow-up period (Fig. 2). In addition to age and depressive symptoms, biochemical markers such as ALT and FPG were also identified as independent predictors of TN incidence among women. Specifically, higher ALT and FPG levels were associated with a greater risk of TNs. These findings were consistent with the results observed in men, where age remained the significant predictor, although with a smaller magnitude of effect compared to women.

Intergroup comparisons

Overall, the Depression-persistent group was significantly associated with TNs incidence compared to the Depression-free group (adjusted HR: 1.848, 95% CI: 1.220–2.801, $p=0.004$).

In men, further intergroup comparisons did not reveal significant differences in TNs incidence. In women, the Depression-persistent group had a significant association with TNs compared to the Depression-free group (adjusted HR: 2.679, 95% CI: 1.513–4.742, $p=0.001$) (Table 5).

Discussion

Our findings suggest a strong association between depression and thyroid health in women, consistent with previous research. Persistent depressive symptoms may increase the risk of developing TNs, highlighting the need for attention to mental health in managing thyroid

Table 3 Baseline and follow-up characteristics of the participants according to depressive symptoms stratified by gender

Parameters	Baseline/	Total participants ($n=818$)				P	Men ($n=571$)				P	Women ($n=247$)				P
	Follow-up	Depression-free	Depression-developed	Depression-recovery	Depression-persistent		Depression-free	Depression-developed	Depression-recovery	Depression-persistent		Depression-free	Depression-developed	Depression-recovery	Depression-persistent	
n		499	95	107	117		380	63	66	62		119	32	41	55	
Male, n (%)		380 (76.15%)	63 (66.32%)	66 (61.68%)	62 (52.99%)	< 0.001										
Follow-up times(years)		2.71 ± 1.75	2.97 ± 1.78	2.91 ± 1.86	2.57 ± 1.73	0.274	2.58 ± 1.71	2.83 ± 1.78	2.65 ± 1.77	2.40 ± 1.91	0.576	3.14 ± 1.82	3.26 ± 1.77	3.34 ± 1.95	2.76 ± 1.49	0.375
Age (years)		32.57 ± 6.61	36.38 ± 8.91	33.49 ± 7.87	35.89 ± 8.09	< 0.001	32.41 ± 6.43	37.33 ± 9.68[a]	32.58 ± 7.61[d]	35.02 ± 8.76[c]	< 0.001	33.07 ± 7.16	34.50 ± 6.90	34.95 ± 8.16	36.87 ± 7.22[c]	0.011
		35.13 ± 7.34	39.57 ± 9.85[a]	36.30 ± 8.59[d]	38.32 ± 8.63[c]	< 0.001	34.79 ± 7.21	40.40 ± 10.68[a]	35.24 ± 8.65[d]	37.13 ± 9.40[c]	< 0.001	36.22 ± 7.68	37.94 ± 7.88	38.00 ± 8.31	39.67 ± 7.54[c]	0.053
Height (cm)	baseline	167.67 ± 7.95	165.01 ± 8.00	164.84 ± 8.49	164.40 ± 8.64	< 0.001	170.44 ± 6.49	169.06 ± 5.73	169.52 ± 6.39	170.10 ± 6.11	0.350	158.81 ± 5.22	157.02 ± 5.41	157.32 ± 5.53	157.98 ± 6.23	0.264
	follow-up	167.99 ± 7.84	165.23 ± 7.96	164.95 ± 8.14	164.65 ± 8.46	< 0.001	170.74 ± 6.41	169.33 ± 5.56	169.54 ± 6.20	170.45 ± 5.74	0.232	159.20 ± 5.03	157.16 ± 5.36	157.55 ± 4.73	158.10 ± 5.84	0.123
Weight (kg)	baseline	69.85 ± 13.51	65.76 ± 12.83	65.99 ± 15.12	64.41 ± 14.31	< 0.001	74.39 ± 11.73	71.59 ± 10.57	73.76 ± 13.09	72.39 ± 12.93	0.266	55.36 ± 7.07	54.27 ± 8.41	53.49 ± 8.21	55.42 ± 9.79	0.565
	follow-up	70.88 ± 13.66	67.23 ± 13.42	66.94 ± 15.24	65.41 ± 13.89	< 0.001	75.61 ± 11.62	73.70 ± 11.00	74.79 ± 13.53	73.34 ± 12.51	0.399	55.78 ± 7.21	54.50 ± 7.21	54.29 ± 7.28	56.47 ± 9.16	0.462
BMI (kg/cm^2)	baseline	24.72 ± 3.71	24.04 ± 3.72	24.08 ± 4.05	23.62 ± 3.69	0.017	25.57 ± 3.51	25.06 ± 3.55	25.61 ± 3.86	24.92 ± 3.53	0.438	21.98 ± 2.93	22.02 ± 3.23	21.61 ± 3.03	22.16 ± 3.31	0.851
	follow-up	24.97 ± 3.70	24.48 ± 3.70	24.39 ± 4.12	23.95 ± 3.65	0.038	25.90 ± 3.47	25.69 ± 3.51	25.95 ± 4.01	25.17 ± 3.62	0.493	22.02 ± 2.75	22.08 ± 2.79	21.89 ± 2.91	22.56 ± 3.19	0.636
SBP (mmHg)	baseline	123.86 ± 14.36	122.51 ± 14.35	122.22 ± 14.21	120.53 ± 14.18	0.128	127.39 ± 13.50	125.56 ± 15.07	128.70 ± 12.48	127.48 ± 12.16	0.616	112.55 ± 10.73	116.50 ± 10.69	111.80 ± 10.10	112.69 ± 12.12	0.264
	follow-up	121.78 ± 15.08	121.81 ± 17.40	118.39 ± 14.92	118.14 ± 15.04	0.035	124.48 ± 15.02	124.89 ± 17.82	123.21 ± 13.94	125.00 ± 13.98	0.901	113.78 ± 11.73	115.75 ± 15.00	110.63 ± 13.19	110.40 ± 12.24	0.179
DBP (mmHg)	baseline	74.39 ± 10.57	74.42 ± 10.75	73.23 ± 9.34	72.17 ± 8.97	0.159	76.38 ± 10.58	76.95 ± 10.25	76.24 ± 9.13	75.58 ± 7.73	0.898	68.06 ± 7.67	69.44 ± 10.09	68.39 ± 7.54	68.33 ± 8.76	0.872
	follow-up	74.20 ± 11.14	74.38 ± 11.71	71.62 ± 10.69	71.04 ± 10.39	0.010	76.17 ± 11.22	76.86 ± 11.74	75.26 ± 10.48	75.35 ± 9.92	0.810	67.92 ± 8.15	69.50 ± 10.14	65.76 ± 9.19	66.18 ± 8.68	0.175
FPG (mmol/L)	baseline	5.17 ± 0.79	5.36 ± 1.04	5.33 ± 1.08	5.34 ± 0.98	0.064	5.20 ± 0.86	5.45 ± 1.22	5.39 ± 1.34	5.44 ± 1.23	0.089	5.07 ± 0.50	5.18 ± 0.53	5.21 ± 0.41	5.23 ± 0.57	0.180
	follow-up	5.24 ± 1.09	5.50 ± 1.55	5.26 ± 0.92	5.35 ± 1.17	0.209	5.33 ± 1.20	5.69 ± 1.84[a]	5.42 ± 1.08	5.55 ± 1.50	0.160	4.95 ± 0.52	5.10 ± 0.44	4.99 ± 0.51	5.12 ± 0.56[c]	0.168
TG (mmol/L)	Baseline	1.53 ± 1.13	1.65 ± 1.80	1.60 ± 1.53	1.45 ± 1.03	0.661	1.68 ± 1.14	2.03 ± 2.10	1.94 ± 1.76	1.75 ± 1.09	0.185	1.02 ± 0.94	0.91 ± 0.42	1.06 ± 0.79	1.12 ± 0.83	0.731
	follow-up	1.69 ± 1.21	1.81 ± 1.49	1.56 ± 1.11	1.47 ± 0.85	0.133	1.90 ± 1.27	2.14 ± 1.64	1.81 ± 1.24	1.71 ± 0.84	0.260	1.04 ± 0.69	1.14 ± 0.79	1.15 ± 0.71	1.19 ± 0.77	0.533
TCH (mmol/L)	baseline	5.04 ± 0.89	5.05 ± 1.08	5.07 ± 1.13	4.88 ± 0.96	0.381	5.12 ± 0.90	5.24 ± 1.14	5.37 ± 1.13	5.13 ± 0.88	0.235	4.77 ± 0.80	4.67 ± 0.83	4.59 ± 0.96	4.59 ± 0.98	0.510
	follow-up	5.25 ± 0.97	5.29 ± 1.11	5.20 ± 1.02	5.06 ± 0.89	0.235	5.34 ± 0.98	5.46 ± 1.18	5.41 ± 1.11	5.26 ± 0.87	0.689	4.96 ± 0.88	4.96 ± 0.89	4.87 ± 0.77	4.83 ± 0.87	0.775
LDL-C (mmol/L)	baseline	3.04 ± 0.74	3.01 ± 1.00	2.95 ± 0.89	2.88 ± 0.90	0.245	3.16 ± 0.71	3.16 ± 1.08	3.15 ± 0.91	3.16 ± 0.88	1.000	2.65 ± 0.69	2.72 ± 0.75	2.62 ± 0.76	2.56 ± 0.82	0.801
	follow-up	3.29 ± 0.76	3.23 ± 0.90	3.17 ± 0.87	3.12 ± 0.78	0.129	3.40 ± 0.74	3.39 ± 0.95	3.38 ± 0.94	3.37 ± 0.73	0.983	2.94 ± 0.71	2.93 ± 0.71	2.83 ± 0.64	2.84 ± 0.75	0.765
HDL-C (mmol/L)	baseline	1.34 ± 0.27	1.35 ± 0.24	1.39 ± 0.31	1.39 ± 0.31	0.219	1.28 ± 0.24	1.29 ± 0.25	1.34 ± 0.33	1.29 ± 0.29	0.285	1.56 ± 0.25	1.47 ± 0.20	1.47 ± 0.28	1.50 ± 0.30	0.144
	follow-up	1.29 ± 0.28	1.31 ± 0.27	1.33 ± 0.30	1.33 ± 0.28	0.234	1.21 ± 0.24	1.23 ± 0.22	1.27 ± 0.27	1.24 ± 0.25	0.346	1.52 ± 0.30	1.46 ± 0.31	1.44 ± 0.32	1.43 ± 0.28	0.246
UA (μmol/L)	baseline	395.48 ± 103.31	364.53 ± 92.95	374.29 ± 101.94	369.33 ± 112.31	0.006	429.02 ± 87.85	405.42 ± 81.50	419.84 ± 95.35	425.98 ± 115.31	0.280	288.38 ± 71.17	284.03 ± 53.16	300.96 ± 61.87	305.46 ± 65.08	0.302
	follow-up	418.79 ± 112.05	388.97 ± 102.02	390.30 ± 117.56	379.81 ± 114.70	0.001	455.35 ± 96.35	428.79 ± 95.64[a]	450.09 ± 100.67	440.58 ± 110.63	0.204	302.07 ± 71.56	310.56 ± 60.77	294.05 ± 68.99	311.30 ± 73.60	0.620
ALT (U/L)	baseline	37.93 ± 31.35	32.92 ± 19.82	35.32 ± 26.49	35.04 ± 30.76	0.391	43.33 ± 33.56	40.73 ± 22.83	43.41 ± 29.08	46.44 ± 37.01	0.809	20.68 ± 11.68	19.75 ± 8.88	22.30 ± 14.28	22.18 ± 12.94	0.711
	follow-up	36.77 ± 31.12	31.15 ± 28.26	32.42 ± 26.76	33.90 ± 39.77	0.303	42.36 ± 34.45	38.52 ± 31.84	42.58 ± 29.60	48.14 ± 50.25	0.508	18.93.68 ± 10.96	16.66 ± 8.18	16.31 ± 6.60	17.85 ± 7.07	0.353
AST (U/L)	baseline	25.90 ± 15.06	25.39 ± 8.00	25.13 ± 11.27	25.61 ± 13.43	0.951	26.96 ± 12.73	27.27 ± 8.52	27.53 ± 12.24	30.18 ± 15.73	0.327	22.50 ± 20.52	21.68 ± 5.26	21.25 ± 8.26	20.45 ± 7.54	0.866
	follow-up	25.36 ± 13.14	23.83 ± 10.38	25.32 ± 13.22	25.52 ± 16.71	0.770	26.96 ± 14.38	26.32 ± 11.66	29.43 ± 15.16	30.94 ± 20.74	0.161	20.26 ± 5.44	18.94 ± 4.16	18.81 ± 4.49	19.42 ± 6.51	0.373
GGT (U/L)	baseline	34.10 ± 26.93	36.65 ± 30.09	35.11 ± 30.68	34.07 ± 28.28	0.863	39.25 ± 28.60	46.16 ± 32.25	44.61 ± 34.73	46.57 ± 32.64	0.111	17.65 ± 8.64	17.94 ± 10.92	19.82 ± 12.08	18.53 ± 10.23	0.438
	follow-up	36.48 ± 25.76	42.81 ± 48.25	37.17 ± 39.08	36.62 ± 34.78	0.372	41.93 ± 26.70	59.35 ± 69.32[a]	49.59 ± 45.49	51.33 ± 41.81	0.003	18.09 ± 10.58	16.49 ± 7.73	17.47 ± 7.07	20.04 ± 9.81	0.305
Cr (μmol/L)	baseline	68.77 ± 12.09	68.01 ± 13.60	67.22 ± 11.80	65.18 ± 12.46	0.037	72.91 ± 10.18	74.94 ± 10.78	73.25 ± 9.80	72.06 ± 11.15	0.427	55.54 ± 7.24	54.38 ± 6.26	57.53 ± 7.54	57.43 ± 8.83	0.143

Table 3 (continued)

Parameters	Baseline/	Total participants ($n=818$)				P	Men ($n=571$)				P	Women ($n=247$)				P
	Follow-up	Depression-free	Depression-developed	Depression-recovery	Depression-persistent		Depression-free	Depression-developed	Depression-recovery	Depression-persistent		Depression-free	Depression-developed	Depression-recovery	Depression-persistent	
	follow-up	73.83 ± 13.52	70.45 ± 16.29	70.38 ± 13.69	68.42 ± 15.26	< 0.001	78.68 ± 10.80	78.31 ± 13.85	78.22 ± 9.92	76.91 ± 14.63	0.736	58.34 ± 8.91	54.98 ± 6.97	57.77 ± 8.50	58.84 ± 9.07	0.205
FT3 (pmol/L)	baseline	4.99 ± 0.57	5.12 ± 0.57	5.06 ± 0.28	5.07 ± 0.67	0.944	5.05 ± 0.60	5.25 ± 0.55	4.99 ± 0.27	5.13 ± 0.71	0.853	4.72 ± 0.32	4.90 ± 0.57	5.26 ± 0.28	4.69 ± 0.51	0.613
	follow-up	5.07 ± 0.42	5.01 ± 0.50	4.94 ± 0.34	5.16 ± 0.77	0.864	5.20 ± 0.40	5.06 ± 0.50	5.10 ± 0.23	5.26 ± 0.84	0.969	4.89 ± 0.39	5.00 ± 0.57	4.74 ± 0.39	4.77 ± 0.18	0.850
FT4 (pmol/L)	baseline	16.76 ± 2.69	16.26 ± 1.69	17.00 ± 1.92	15.97 ± 1.95	0.388	17.04 ± 2.80	16.92 ± 0.73	17.00 ± 1.99	15.96 ± 2.10	0.454	15.43 ± 1.99	15.15 ± 2.39	17.00 ± 2.11	16.00 ± 1.70	0.613
	follow-up	16.83 ± 2.57	16.33 ± 1.75	16.19 ± 136	17.85 ± 2.15	0.362	17.75 ± 2.71	18.19 ± 1.59	15.74 ± 0.94	17.49 ± 2.24	0.511	15.44 ± 1.83	15.96 ± 1.69	16.79 ± 1.80	19.32 ± 1.17	0.117
TSH (mIU/L)	baseline	1.79 ± 1.64	1.67 ± 0.86	1.69 ± 0.38	1.80 ± 1.53	0.803	1.82 ± 0.54	1.58 ± 0.47	1.62 ± 0.32	1.82 ± 1.57	0.117	1.75 ± 0.55	1.81 ± 1.34	1.87 ± 0.65	1.62 ± 0.57	0.850
	follow-up	2.05 ± 1.58	2.02 ± 1.49	1.93 ± 2.09	1.88 ± 0.56	0.458	2.09 ± 1.55	1.88 ± 0.67	1.67 ± 0.33	1.77 ± 0.54	0.493	1.98 ± 0.88	2.13 ± 0.93	1.99 ± 0.69	1.84 ± 0.88	0.915
SDS score	baseline	35.77 ± 6.75	36.04 ± 6.17	56.09 ± 4.52[bd]	56.99 ± 5.06[ce]	< 0.001	36.58 ± 6.91	26.39 ± 6.47	55.76 ± 4.10[bd]	57.48 ± 4.96[ce]	< 0.001	35.84 ± 6.21	35.33 ± 5.56	56.62 ± 5.15[bd]	56.44 ± 5.17[ce]	< 0.001
	follow-up	36.13 ± 6.49	52.59 ± 2.85[a]	43.94 ± 4.23[bd]	57.33 ± 5.16[cef]	< 0.001	35.99 ± 6.68	52.88 ± 2.87[a]	42.77 ± 4.14[bd]	57.64 ± 5.15[cef]	< 0.001	36.55 ± 5.89	51.99 ± 2.78[a]	45.80 ± 3.69[bd]	57.00 ± 5.19[cef]	< 0.001

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; UA, uric acid; ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; Cr, creatinine; FT3, free triiodothyronine; FT4, free tetraiodothyronine; TSH, thyroid stimulating hormone; SDS, Zung self-rating depression scale; TNs, thyroid nodules

a group depression-developed vs. group depression-free, $p<0.05$

b group depression-recovery vs. group depression-free, $p<0.05$

c group depression-persistent vs. group depression-free, $p<0.05$

d group depression-recovery vs. group depression-developed, $p<0.05$

e group depression-persistent vs. group depression-developed, $p<0.05$

f group depression-persistent vs. group depression-recovery, $p<0.05$

Table 4 Univariate and multivariate COX regressions analysis of risk factors for TNs according to the dynamic changes of depressive symptoms

Mental Status	Incidence Rate per 100 Person-Years	Univariate analysis		Multivariate analysis*	
		HR (95%CI)	*P*	HR (95%CI)	*P*
Total participants					
Depression-free	5.31	1 (reference)		1 (reference)	
Depression-developed	5.67	1.004 (0.584–1.725)	0.99	0.891 (0.517–1.534)	0.676
Depression-recovery	7.38	1.307 (0.818–2.089)	0.263	1.161 (0.724–1.866)	0.533
Depression-persistent	11.66	2.165 (1.447–3.241)	< 0.001	1.857 (1.229–2.805)	0.003
Men					
Depression-free	4.89	1 (reference)			
Depression-developed	5.06	0.997 (0.489–2.034)	0.994		
Depression-recovery	6.86	1.408 (0.747–2.654)	0.289		
Depression-persistent	6.73	1.289 (0.647–2.566)	0.47		
Women					
Depression-free	6.43	1 (reference)		1 (reference)	
Depression-developed	6.71	0.997 (0.430–2.310)	0.994	1.108 (0.439–2.364)	0.966
Depression-recovery	8.04	1.164 (0.572–2.367)	0.676	1.141 (0.561–2.322)	0.716
Depression-persistent	16.48	2.771 (1.583–4.850)	< 0.001	2.560 (1.454–4.508)	0.001

HR, hazard ratio; CI, confidence interval; TNs, thyroid nodules

*Adjusted for gender, age and BMI in total participants. *Adjusted for age in women

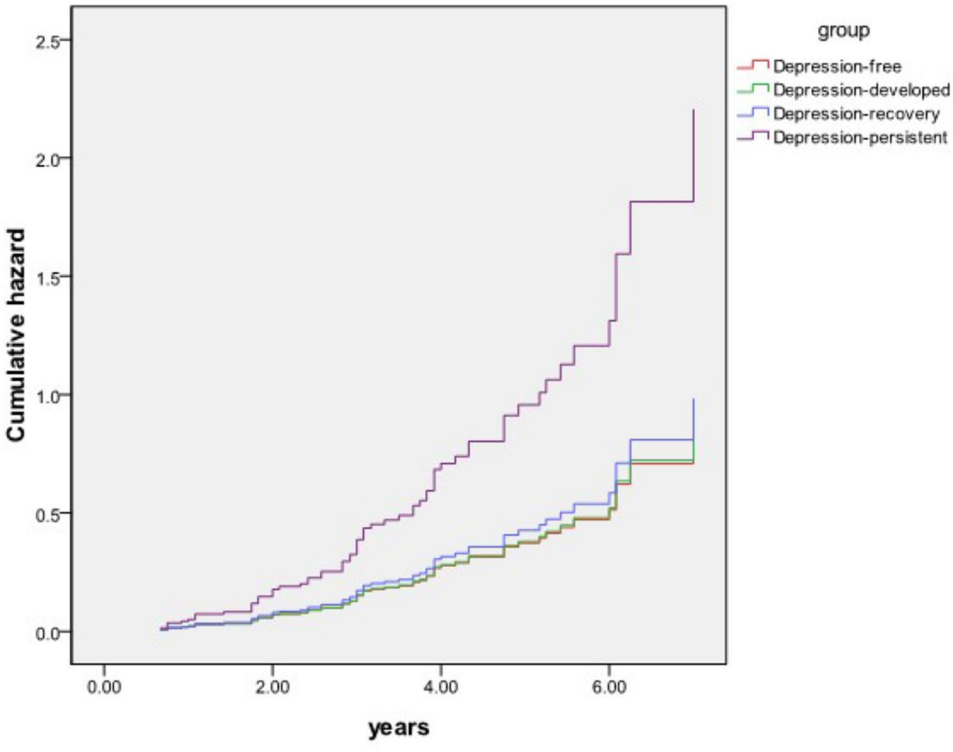

Fig. 2 Age adjusted curves showing the cumulative hazards of TNs among the study groups in women

conditions. The identification of factors such as age and ALT suggests that both metabolic and psychological variables contribute to TN risk. Consistent with prior research [23, 24], our study found that TNs are more prevalent in women. In addition to known factors such as thyroid dysfunction [25] and the presence of positive antithyroid antibodies [26], an increased risk of TNs appears to be an additional thyroid abnormality associated with depression.

In depressed patients, there is often hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and elevated cortisol levels [27, 28]. Depression is also associated with increased levels of inflammatory markers, including C-reactive protein, interleukin (IL)-1, and IL-6 [29].

Table 5 Comparison of TN risk among the four groups

Compared Subgroups	Adjusted HR(95%CI)*	*P*
Total participants		
Depression-developed vs. Depression-free	0.894 (0.518–1.543)	0.687
Depression-recovery vs. Depression-free	1.175 (0.730–1.890)	0.506
Depression-persistent vs. Depression-free	1.848 (1.220–2.801)	0.004
Depression-recovery vs. Depression-developed	1.340 (0.704–2.549)	0.373
Depression-persistent vs. Depression-developed	2.018 (1.109–3.675)	0.022
Depression-recovery vs. Depression-persistent	0.632 (0.372–1.073)	0.089
Men		
Depression-developed vs. Depression-free	0.857 (0.415–1.770)	0.676
Depression-recovery vs. Depression-free	1.231 (0.650–2.333)	0.523
Depression-persistent vs. Depression-free	1.200 (0.602–2.391)	0.605
Depression-recovery vs. Depression-developed	1.464 (0.611–3.505)	0.392
Depression-persistent vs. Depression-developed	1.187(0.468–3.010)	0.718
Depression-recovery vs. Depression-persistent	1.022 (0.440–2.372)	0.960
Females		
Depression-developed vs. Depression-free	0.993 (0.427–4.860)	0.988
Depression-recovery vs. Depression-free	1.133 (0.557–2.308)	0.730
Depression-persistent vs. Depression-free	2.679 (1.513–4.742)	0.001
Depression-recovery vs. Depression-developed	1.076 (0.409–2.829)	0.882
Depression-persistent vs. Depression-developed	2.445 (1.064–5.714)	0.039
Depression-recovery vs. Depression-persistent	0.445 (0.216–0.913)	0.027

TNs, thyroid nodules; HR, hazard ratio; CI, confidence interval

*Adjusted for gender, age and BMI in total participants. Adjusted for age in men and women

Elevated cortisol and inflammatory markers can disrupt metabolic signaling pathways, leading to insulin resistance. Insulin resistance and hyperinsulinemia are commonly observed in individuals with depressive symptoms [30]. Hyperinsulinemia, through its mitogenic effects, may promote the development and growth of TNs as well as the proliferation of thyroid follicular cells [31]. Additionally, individuals with depression are more likely to engage in unhealthy lifestyle habits such as physical inactivity, excessive alcohol consumption, smoking, poor diet, and obesity [32], which may indirectly contribute to the occurrence of TNs. Although depression is often associated with these factors, which could potentially influence the development of TNs, our study did not directly measure these variables. Future studies should incorporate these factors to provide a more comprehensive understanding of their impact.

After a mean follow-up period of 2.75 years, our study found that women with persistent depression showed a significantly increased risk of TNs compared to women without depression, while no other significant changes of TN risk were found between other groups, suggesting that persistent depression may have a cumulative long-term effect on TN development, indicating the need for prolonged follow-up studies. This finding is also in correlation with some previous studies, Wang et al. revealed that persistent depression was an independent risk factor for many diseases including heart, lung, kidney, memory diseases et al. [33], however that study did not include thyroid-related diseases for analysis. Out study also revealed that P value in some groups were less than 0.05, however, after Bonferroni correction, there was still no significant difference.

Preventing TNs is important due to their potential progression to thyroid cancer and the impact they can have on thyroid function. Although many TNs are benign, some may harbor malignancy, making early detection and prevention crucial for effective management. Additionally, TNs can lead to symptoms such as difficulty swallowing or changes in thyroid hormone levels, which can significantly affect a patient's quality of life. Early screening and intervention for depression could, therefore, be part of a broader strategy to monitor and manage thyroid health, potentially reducing the incidence of TNs and their associated complications. The study also revealed gender differences: while an association between depressive symptoms and TN development was observed in women, no such association was found in men.

Depression and age emerged as significant risk factors for TNs, particularly in women. Although FPG levels differed slightly between depressive and non-depressive women, the overall effect of metabolic factors on TN risk appears limited, suggesting that psychological health plays a more prominent role. Additionally, men in our cohort had higher levels of TC, LDL, and FPG compared to women. This difference in general health status between genders may play a role in the differing risk profiles for TNs. While age remained the most significant predictor for TNs in men, their poorer general metabolic health may influence the overall risk of TN development. These findings suggest that gender-specific health profiles, including lipid and glucose levels, could be important factors in understanding the gender differences in TN prevalence and depressive symptom-related risks. Women, who are more prone to both depression and thyroid disorders, were shown in several studies to have a 50–60% higher likelihood of developing depressive symptoms when diagnosed with TNs, compared to men. Postmenopausal women with TNs showed a higher prevalence of depressive symptoms, possibly due to hormonal shifts and their impact on thyroid function.

Estradiol, a hormone known to promote thyroid cell growth [34], has been identified as a potent growth factor for both benign and malignant thyroid cells [35, 36]. Our

findings suggest that gender differences and hormonal factors play a significant role in the observed outcomes. Previous research has shown that hormonal fluctuations, such as those associated with menstrual cycles, pregnancy, and menopause, can impact thyroid function and related health conditions. For instance, women are more likely to develop autoimmune thyroid diseases, such as Hashimoto thyroiditis, partly due to hormonal variations. However, existing research has shown that serum estradiol levels are decreased in females and elevated in males with depression [37, 38], which appears contradictory to our findings. Additionally, gender-specific differences in metabolism and hormonal regulation may contribute to variations in disease progression and symptomatology. Further research incorporating sex hormones is needed to clarify the role of hormonal differences in the relationship between depressive symptoms and the risk of TNs.

To our knowledge, this is the first prospective study investigating the association between mental status and TN risk. Nevertheless, there are some limitations to this study. First, the participants were individuals who chose to undergo regular health examinations, potentially introducing selection bias. Second, while SDS is a widely used screening tool for detecting depression in the general population, it is not a diagnostic instrument. Therefore, our findings may not be applicable to patients with clinically diagnosed depression. Third, the study was limited by its small sample size and relatively short follow-up period. Future research should address several critical areas to advance our understanding of thyroid health. Large-scale, prospective studies with extended follow-up are essential to evaluate the long-term effects of depression on TNs and thyroid cancers. Additionally, longitudinal research involving diverse populations is needed to examine how hormonal fluctuations during different life stages, such as puberty, pregnancy, and menopause, impact thyroid health and disease progression. Investigating the interactions between hormonal therapies and thyroid disorders could further refine personalized treatment strategies. Multi-center trials with standardized protocols are recommended to enhance the generalizability of findings and mitigate variability across settings. Lastly, future studies should explore additional factors, such as lifestyle, insulin resistance, and sex hormones, which were not addressed in the current research.

Nevertheless, the clinical implications of our study highlight the potential value of regular thyroid screening in women with persistent depressive symptoms. Given the association between chronic depression and an increased risk of TNs, early detection and monitoring of thyroid health in this population may prevent the progression of TNs and reduce the risk of more serious thyroid conditions, including cancer. Additionally, our findings suggest that successful management of depression may lower the risk of TNs, reinforcing the importance of timely and effective mental health interventions. These results support an integrated approach to patient care, where both mental and physical health are monitored, particularly in women at higher risk for thyroid abnormalities.

Conclusions

The current study demonstrated that women with depressive symptoms are associated with a higher prevalence of TNs. depressive symptoms emerged as an independent risk factor for developing TNs. Additionally, over a mean follow-up period of 2.75 years, persistent depressive symptoms were linked to an increased risk of TNs in total participants and women participants.

Abbreviations

TNs	Thyroid nodules
SDS	Self-Rating Depression Scales
BMI	Body mass index
FPG	Fasting plasma glucose
TG	Triglycerides
TC	Total cholesterol
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
UA	Uric acid
ALT	Alanine transaminase
AST	Aspartate aminotransferase
GGT	Glutamyl transpeptidase
Cr	Creatinine
FT3	Free triiodothyronine
FT4	Free tetraiodothyronine
TSH	Thyroid stimulating hormone
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
HR	Hazard ratio
CIs	Confidence intervals

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Not applicable.

Author contributions

Yan Yang, Qijun Liang, Zhenhong Qi and Shouyi Yu carried out the studies, participated in collecting data, and drafted the manuscript. Qijun Liang and Jue Zhang performed the statistical analysis and participated in its design. Yan Yang, Qijun Liang and Aisheng Wei participated in acquisition, analysis, or interpretation of data and draft the manuscript. All authors read and approved the final manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Foshan Hospital of Traditional Chinese Medicine's Committee on Human Research. Each

participant provided written informed consent. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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