

Prevalence, incidence, and risk factors of thyroid disorders in a southwestern Iranian population: findings from the PERSIAN Dena Cohort Study

Received: 5 July 2026

Accepted: 3 August 2026

Published online: 08 August 2026

Cite this article as: Nejatiyan M., Salehnasab C., Seyed-Nezhad M. *et al.* Prevalence, incidence, and risk factors of thyroid disorders in a southwestern Iranian population: findings from the PERSIAN Dena Cohort Study. *BMC Endocr Disord* (2026). <https://doi.org/10.1186/s12902-026-02464-y>

Marziye Nejatiyan, Cirruse Salehnasab, Maryam Seyed-Nezhad, Morteza Rakhshmah & Mohammad Moradi-Joo

We are providing an unedited version of this manuscript to give early access to its findings. Before final publication, the manuscript will undergo further editing. Please note there may be errors present which affect the content, and all legal disclaimers apply.

If this paper is publishing under a Transparent Peer Review model then Peer Review reports will publish with the final article.

Prevalence, Incidence, and Risk Factors of Thyroid Disorders in a Southwestern Iranian Population: Findings from the PERSIAN Dena Cohort Study

Marziye Nejatiyan¹, Cirruse Salehnasab², Maryam Seyed-Nezhad³, Morteza Rakhshmah⁴, Mohammad Moradi-Joo^{2*}

1. Student Research Committee, Yasuj University of Medical Sciences, Yasuj, Iran.
2. Social Determinants of Health Research Center, Yasuj University of Medical Sciences, Yasuj, Iran.
3. National Center for Health Insurance Research, Tehran, Iran.
4. Clinical Research Development Center, Shahid Jalil Hospital, Yasuj University of Medical Sciences, Yasuj, Iran.

Corresponding author: *Mohammad Moradi-Joo*, Social Determinants of Health Research Center, Yasuj University of Medical Sciences, Yasuj, Iran.

Email: moradi2011@yahoo.com

Abstract

Background: Thyroid disorders are among the most common endocrine conditions worldwide, yet population-based prevalence and incidence data from ethnically distinct, semi-rural regions of Iran remain limited. This study aimed to determine the baseline prevalence, five-year cumulative incidence, and associated risk factors of thyroid disease among adult participants of the PERSIAN Dena Cohort Study (PDCS) in Kohgiluyeh and Boyer-Ahmad Province, southwestern Iran.

Methods: This prospective cohort study used baseline data from 3,203 adults aged 35–70 years to estimate thyroid disease prevalence, and five-year follow-up data from 2,829 disease-free participants to estimate cumulative and annual incidence proportions. Data on demographic, socioeconomic, behavioral, dietary, and clinical factors were collected using standardized questionnaires. Thyroid disease was ascertained based on self-reported physician diagnosis and medication use. Associations were assessed using chi-square and Mann–Whitney U tests, and multivariable logistic regression was used to identify factors associated with prevalent thyroid disease. Annual incidence proportions were calculated based on the population at risk at the beginning of each year. Analyses were performed using IBM SPSS Statistics (version 26), with $p < 0.05$ considered statistically significant.

Results: The baseline prevalence of thyroid disease was 11.7% (374/3,203), and the five-year cumulative incidence among initially disease-free participants was 2,261.48 per 100,000 population, with 64 incident cases identified. Female sex was the strongest independent correlate of thyroid disease (OR = 4.61; 95% CI: 2.83–7.52). History of memory impairment (OR = 1.67), history of depression (OR = 1.47), history of chronic headache (OR = 1.49), kidney stones (OR = 1.29), higher vitamin D intake (IU/day) (OR = 1.08), and lower total trans fatty acid intake (OR = 0.48), although these findings should be interpreted with caution, likely due to reverse causation or residual confounding, were also independently associated with thyroid disease. Thyroid disease was further associated with lower educational attainment, lower physical activity, lower overall dietary energy and micronutrient intake, and a higher prevalence of hypertension, diabetes, and fatty liver disease.

Conclusion: Clinically diagnosed thyroid disease is relatively common in this population, with a higher prevalence observed in certain demographic and clinical subgroups. However, the observed associations are primarily cross-sectional and should not be interpreted as causal. These findings provide descriptive epidemiological insights and may help inform future longitudinal and interventional studies; whether these characteristics can support effective targeted testing strategies requires prospective validation.

Keywords: Thyroid Diseases; Hypothyroidism; Prevalence; Incidence; Cohort Studies; Risk Factors; Iran

1. Introduction

Thyroid disorders, encompassing hypothyroidism, hyperthyroidism, autoimmune thyroiditis, and structural abnormalities such as goiter and thyroid nodules, represent one of the most common groups of endocrine conditions worldwide, with an estimated 200 million people affected globally (1). Population-based surveys have shown that the age-standardized prevalence of thyroid disease among adults has continued to rise in recent decades, with the highest burden observed among older adults and women (1). Beyond their direct clinical manifestations, thyroid disorders are associated with a broad range of adverse outcomes, including cardiovascular disease, dyslipidemia, impaired glucose metabolism, depression, and increased overall mortality, underscoring their relevance as a public health priority rather than a purely clinical concern (2).

The epidemiology of thyroid dysfunction, however, is far from uniform across populations. Global meta-analyses indicate that the prevalence of autoimmune thyroiditis, one of the leading causes of hypothyroidism, varies considerably by geographic region, iodine status, and diagnostic criteria, with pooled estimates reaching approximately 7.5% in adults worldwide (3). Similarly, thyroid nodules have been documented in roughly one in four adults globally, with marked heterogeneity attributable to differences in imaging modality, iodine intake, and population age structure (4). A meta-analysis of European cohorts reported pooled prevalence rates of 3.05% for hypothyroidism and 0.75% for hyperthyroidism (5), while data from Iranian population-based studies have generally reported a higher burden of thyroid dysfunction than western populations, with overt hypo- and hyperthyroidism affecting 2%–2.8% and 0.8%–2.2% of adults, respectively, and subclinical dysfunction being considerably more common (6). More recent Iranian cohorts, such as the Tehran-based HAMRAH study, have documented an overall thyroid dysfunction prevalence of 10.3% among urban adults, with hypothyroidism disproportionately affecting women (6).

A substantial body of evidence has identified female sex, older age, obesity, smoking, family history of thyroid disease, and both iodine deficiency and iodine excess as important determinants of thyroid dysfunction (1,4). Positivity for thyroid peroxidase antibodies (TPOAb) has likewise been established as a strong predictor of incident hypo- and hyperthyroidism, as demonstrated in a six-year prospective cohort from Isfahan, an iodine-sufficient region of Iran, in which the incidence rate of hypothyroidism reached 3.3 and 2.1 per 1000 population in women and men, respectively (7). Despite this accumulating knowledge, most of the available Iranian data are derived from cross-sectional surveys or from cohorts based in large metropolitan centers such as Tehran and Isfahan (6,7), leaving considerable uncertainty about the burden of thyroid disease in less-studied, ethnically distinct, and geographically isolated regions of the country. Data from the Birjand Longitudinal Aging Study, for instance, revealed an age-standardized thyroid dysfunction prevalence of nearly 28% among older adults in eastern Iran, a figure considerably higher than urban estimates and suggestive of important regional variation that remains poorly characterized (8).

Kohgiluyeh and Boyer-Ahmad Province, located in southwestern Iran, is a mountainous, ethnically Lur region with a distinct dietary pattern, environmental exposure profile, and level of healthcare access compared with the major urban centers in which most Iranian thyroid epidemiology has so far been concentrated. To date, no population-based prospective cohort has quantified either the prevalence or the cumulative incidence of thyroid disorders in this population, nor systematically examined the contribution of modifiable and non-modifiable risk factors to disease occurrence over time. This gap is particularly important because cross-sectional prevalence estimates, while informative, cannot capture the dynamic emergence of new cases or clarify the temporal relationship between candidate risk factors and thyroid dysfunction information that only longitudinal, prospective designs can provide (7,9).

The Prospective Epidemiological Research Studies in Iran (PERSIAN) Cohort was established as a nationwide platform to characterize the region-specific burden of non-communicable diseases and their risk factors across Iran's diverse provinces (9). As one of the constituent regional cohorts, the PERSIAN Dena Cohort Study (PDCS) was launched in Dena County, near Yasuj city in Kohgiluyeh and Boyer-Ahmad Province, enrolling adults aged 35–70 years from both urban and rural areas and thereby offering a unique opportunity to investigate thyroid disorders in a previously understudied population (10). Building on the baseline and follow-up data of this cohort, the present study aimed to determine the prevalence and cumulative incidence of thyroid disorders and to identify their associated risk factors among adult participants of the Dena Cohort Study, with the ultimate goal of informing region-specific screening strategies and preventive interventions for thyroid disease in southwestern Iran.

2. Materials and Methods

2.1. Study Design and Setting

This study was designed as a prospective cohort investigation nested within the PDCS, the regional component of the Prospective Epidemiological Research Studies in Iran (PERSIAN) Cohort established in Dena County, near Yasuj city, in Kohgiluyeh and Boyer-Ahmad Province, southwestern Iran. The analysis comprised two complementary components: (a) a baseline cross-sectional component describing the prevalence of thyroid disorders and their associated demographic, behavioral, dietary, and clinical correlates at enrollment, and (b) a longitudinal component describing the five-year cumulative and annual incidence of thyroid disorders among participants who were free of thyroid disease at baseline.

2.2. Study Population

Adults aged 35–70 years residing in urban and rural areas of Dena County were invited to participate during the enrollment phase of the PDCS. After the exclusion of participants with missing data on thyroid disease status, 3,203 participants were included in the baseline prevalence analysis. For the incidence analysis, 2,829 participants who were free of thyroid

disease at enrollment were followed annually over a five-year period to identify newly diagnosed (incident) cases of thyroid disorder.

2.3. Data Collection

Data were collected using standardized, interviewer-administered questionnaires and physical and laboratory examinations conducted by trained personnel at the PDCS enrollment centers, in accordance with the core PERSIAN Cohort protocol. The questionnaires used in this study were not developed specifically for this research; rather, they are part of the standardized and previously validated instruments of the PERSIAN Cohort (9).

Demographic and socioeconomic characteristics included place of residence, sex, age, marital status, and educational level. Socioeconomic status was assessed using a composite Wealth/Socioeconomic Status Index (WSI). Behavioral factors such as smoking, substance use, and alcohol consumption were obtained through the standardized PERSIAN questionnaires. Physical activity was assessed using the validated Persian version of the International Physical Activity Questionnaire (IPAQ), expressed as metabolic equivalent task (MET) scores.

Anthropometric measurements (height and weight) were obtained using calibrated instruments. Dietary intake was assessed using a validated semi-quantitative food frequency questionnaire (FFQ) integrated into the PERSIAN cohort framework, and nutrient intakes were estimated using standard food composition tables.

Information on clinical symptoms and physician-diagnosed chronic diseases was collected via structured interviews based on the PERSIAN cohort questionnaires and, where possible, verified using medical records.

2.4. Case Ascertainment for Thyroid Disorders

Thyroid disease was defined as a composite outcome including previously diagnosed or treated thyroid conditions, such as hypothyroidism, hyperthyroidism, autoimmune thyroiditis, goiter, and thyroid nodules. Thyroid disease status (present/absent) was ascertained at baseline and at each annual follow-up visit through a combination of self-reported physician diagnosis and current use of thyroid-related medication (e.g., levothyroxine or antithyroid drugs). Where available, supporting medical documentation was reviewed.

Information on thyroid medication use was obtained through self-report using standardized cohort questionnaires administered by trained interviewers. Participants were asked to report current and past medication use, and when available, medication use was cross-checked against medication containers or prescriptions presented at the time of the interview.

Participants free of thyroid disease at enrollment were followed prospectively, and incident cases were defined as new self-reported physician diagnoses or initiation of thyroid-related treatment

during follow-up, identified using the same case-ascertainment procedure at subsequent annual visits.

In the absence of systematic biochemical measurements (e.g., serum TSH and free T4) for the entire cohort, the outcome primarily reflects clinically recognized or treated thyroid disease rather than the total burden of thyroid dysfunction.

2.5. Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics of the study population, with categorical variables presented as frequencies and percentages and continuous variables as means with standard deviations or, where distributions departed from normality, as medians with mean ranks. Annual incidence was calculated as the number of new cases divided by the population at risk at the beginning of each year and is therefore interpreted as an annual incidence proportion (risk), expressed per 100,000 population.

The chi-square test was used to examine associations between categorical demographic and behavioral variables and thyroid disease status. The Mann–Whitney U test was used to compare age, socioeconomic status (WSI), physical activity level (MET score), and dietary energy, macronutrient, and micronutrient intakes between participants with and without thyroid disease, given the non-normal distribution of these variables. Dietary variables were analyzed as absolute intakes and were not adjusted for total energy intake.

Multivariable logistic regression analysis was performed to identify factors independently associated with prevalent thyroid disease. The multivariable analysis was conducted using baseline thyroid disease status and therefore represents a cross-sectional assessment of factors associated with prevalent disease. Candidate variables included demographic (age, sex, educational level, socioeconomic status), behavioral (physical activity, smoking, substance use), dietary (energy, macronutrients, micronutrients, including vitamin D intake [IU/day] and trans fatty acid intake [g/day]), and clinical variables (hypertension, diabetes, fatty liver disease, kidney stones, depression, memory impairment, and chronic headache).

Variables with $p < 0.25$ in univariable analysis, together with key covariates selected based on prior literature and clinical relevance (including age and sex), were included in the multivariable model. No automated stepwise selection procedures were applied.

Variables with $p < 0.25$ in univariable analysis, together with key covariates selected based on prior literature and clinical relevance (including age and sex), were included in the multivariable model. Univariable analyses were considered exploratory and were primarily used to identify candidate variables for inclusion in the multivariable model. No automated stepwise selection procedures were applied.

The final model was estimated using complete-case analysis, including participants with no missing data for the variables entered into the model. Multicollinearity among covariates was assessed using variance inflation factors, and no evidence of problematic multicollinearity was observed. The functional form of continuous variables was assessed and retained as linear terms based on model diagnostics.

Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported. All statistical analyses were performed using SPSS software (version 26), and a two-sided p -value < 0.05 was considered statistically significant.

3. Results

3.1. Study Population and Baseline Characteristics

Of the 3,203 participants with available data, 374 (11.7%) were classified as having thyroid disease, while 2,829 (88.3%) were disease-free. Participants without thyroid disease at baseline ($n = 2,829$) were subsequently included in the incidence analysis. The flow of participants through the study, including baseline inclusion and follow-up over five years, is presented in Figure 1.

Figure 1. Participant Flow Diagram of the PERSIAN Dena Cohort Study for Prevalence and Incidence Analyses of Thyroid Disorders

3.2. Incidence of Thyroid Disorders

Among the 2,829 participants who were free of thyroid disease at baseline, a total of 64 incident cases were identified over the five-year follow-up period. This corresponds to a cumulative incidence proportion of 2,262.28 per 100,000 population (95% CI: 1,714–2,810).

Annual incidence proportions varied across follow-up years. In the first year, 16 new cases were identified among 2,829 participants at risk (565.57 per 100,000; 95% CI: 290–840). In the second year, 20 new cases occurred among 2,813 participants (711.16 per 100,000; 95% CI: 400–1,020). In the third year, 18 new cases were observed among 2,793 participants (644.58 per 100,000; 95% CI: 350–940). In the fourth year, 7 new cases were identified among 2,775 participants (252.25 per 100,000; 95% CI: 65–439), and in the fifth year, 3 new cases were observed among 2,768 participants (108.37 per 100,000; 95% CI: 0–231). The fifth-year estimate is based on incomplete follow-up and should be interpreted with caution, as it may underestimate the true incidence for that year. Detailed annual and cumulative incidence estimates, including 95% confidence intervals, are presented in Table 1.

Table 1. Annual Incidence Proportions of Thyroid Disorders in the Study Population over Five Years of Follow-up

Year	Population at risk (start of year), n	New cases, n	Incidence proportion (per 100,000)	95% CI
Year 1	2829	16	565.57	290 – 840
Year 2	2813	20	711.16	400 – 1,020
Year 3	2793	18	644.58	350 – 940
Year 4	2775	7	252.25	65 – 439
Year 5	2768	3	108.37	0 – 231
Total (5-year cumulative)	2829	64	2262.28	1,714 – 2,810

Note: The fifth-year estimate is based on incomplete follow-up and may underestimate the true annual incidence.

3.3. Demographic Characteristics of Incident Cases

Among the 64 participants who developed incident thyroid disorders during follow-up, the majority resided in urban areas (65.6%; $n = 42$), while 34.4% ($n = 22$) resided in rural areas. Women accounted for the large majority of incident cases (81.3%; $n = 52$), compared with 18.8% ($n = 12$) among men. With respect to marital status, most incident cases were married (84.4%; $n = 54$), followed by single and widowed participants (6.3% each; $n = 4$), and divorced participants (3.1%; $n = 2$). Regarding educational attainment, the highest proportions of incident cases had primary-level education (28.1%; $n = 18$) or no formal education (25.0%; $n = 16$), whereas the lowest proportion held a bachelor's degree (6.3%; $n = 4$); none of the incident cases held a postgraduate degree (Table 2).

Table 2. Descriptive Characteristics of Incident Thyroid Disease Cases ($n = 64$)

Variable	Category	n	%
Residence	Urban	42	65.6
	Rural	22	34.4
	Total	64	100.0
Sex	Male	12	18.8
	Female	52	81.3
	Total	64	100.0
Marital status	Single	4	6.3
	Married	54	84.4
	Widowed	4	6.3

Variable	Category	n	%
Educational level	Divorced	2	3.1
	Total	64	100.0
	Illiterate	16	25.0
	Primary	18	28.1
	Middle school	10	15.6
	Diploma	9	14.1
	Associate degree	7	10.9
	Bachelor's degree	4	6.3
	Master's degree or higher	0	0.0
	Total	64	100.0

Note: Values represent descriptive characteristics of incident cases only and do not reflect subgroup-specific incidence rates, as population-at-risk denominators are not incorporated.

3.4. Comparison of Age, Socioeconomic Status, and Physical Activity by Thyroid Disease Status

Median age did not differ significantly between participants with and without thyroid disease (51 [44–58] vs. 50 [43–57] years; Mann–Whitney $U = 504,569.5$, $p = 0.146$). Similarly, the total WSI score was comparable between the two groups (29 [25–33] vs. 28 [24–32]; Mann–Whitney $U = 512,328.0$, $p = 0.502$). In contrast, total physical activity level (MET score) was significantly lower among participants with thyroid disease than among those without (39 [35–42] vs. 40 [36–44]; Mann–Whitney $U = 490,990.50$, $Z = -2.263$, $p = 0.024$). These findings suggest a possible association between lower physical activity and thyroid disease; however, causal inference cannot be drawn from this cross-sectional comparison (Table 3).

Table 3. Comparison of Age, Socioeconomic Status Index (WSI), and Physical Activity Level (MET) between Participants with and without Thyroid Disease (Mann–Whitney U Test)

Variable	Thyroid disease	n	Median (IQR)	U	Z	p-value
Age (years)	Absent	2829	50 (43–57)	504569.5	—	0.146
	Present	374	51 (44–58)			
WSI (total) ^a	Absent	2807	28 (24–32)	512328.0	—	0.502
	Present	373	29 (25–33)			
MET (total) ^b	Absent	2829	40 (36–44)	490990.50	-2.263	0.024

Variable	Thyroid disease	n	Median (IQR)	U	Z	p-value
	Present	374	39 (35–42)			

^a WSI: composite socioeconomic status index used in the PERSIAN Dena Cohort Study; higher scores reflect higher socioeconomic status.

^b MET: total physical activity score derived from the International Physical Activity Questionnaire (IPAQ).

Note: Continuous variables are presented as median (interquartile range) due to non-normal distribution.

3.5. Association of Demographic and Behavioral Factors with Thyroid Disease

Chi-square analysis showed a statistically significant association between sex and thyroid disease status ($\chi^2 = 161.43$, $df = 1$, $p < 0.001$): women accounted for 87.4% of prevalent cases, compared with 12.6% among men. Educational level was also significantly associated with thyroid disease ($\chi^2 = 23.26$, $df = 6$, $p = 0.001$), with the highest prevalence observed among illiterate participants (30.7%) and those with primary-level education (29.4%), and the lowest prevalence among participants with a university education.

With regard to health-related behaviors, current cigarette smoking was significantly associated with thyroid disease status ($\chi^2 = 70.11$, $df = 1$, $p < 0.001$); the prevalence of thyroid disease was considerably higher among non-smokers (14.4%) than among smokers (3.4%). A history of smoking initiation during childhood was also significantly associated with thyroid disease ($\chi^2 = 6.04$, $df = 1$, $p = 0.014$), with a higher prevalence among participants without such a history. No significant association was observed between smokeless tobacco use and thyroid disease status ($\chi^2 = 0.12$, $df = 1$, $p = 0.725$).

Substance use was significantly associated with a lower prevalence of thyroid disease ($\chi^2 = 27.10$, $df = 1$, $p < 0.001$): 2.8% of substance users had thyroid disease, compared with 12.7% of non-users. Similarly, alcohol consumption was significantly associated with a lower prevalence of thyroid disease ($\chi^2 = 15.98$, $df = 1$, $p < 0.001$), affecting 3.0% of alcohol users compared with 12.3% of non-users (Table 4).

Table 4. Association between Demographic and Behavioral Variables and Thyroid Disease Status (Chi-square Test)

Variable	Category	Without thyroid disease, n (%)	With thyroid disease, n (%)	Total, n (%)	χ^2	df	p-value
Sex	Male	1335 (47.2)	47 (12.6)	1382 (43.1)	161.43	1	<0.001

Variable	Category	Without thyroid disease, n (%)	With thyroid disease, n (%)	Total, n (%)	χ^2	df	p-value
	Female	1494 (52.8)	327 (87.4)	1821 (56.9)			
	Total	2829 (100.0)	374 (100.0)	3203 (100.0)			
Educational level	Illiterate	698 (24.7)	115 (30.7)	813 (25.4)	23.26	6	0.001
	Primary	654 (23.1)	110 (29.4)	764 (23.9)			
	Middle school	397 (14.0)	36 (9.6)	433 (13.5)			
	Diploma	525 (18.6)	46 (12.3)	571 (17.8)			
	Associate degree	190 (6.7)	24 (6.4)	214 (6.7)			
	Bachelor's degree	299 (10.6)	37 (9.9)	336 (10.5)			
	Postgraduate degree	66 (2.3)	6 (1.6)	72 (2.2)			
	Total	2829 (100.0)	374 (100.0)	3203 (100.0)			
Current cigarette smoking	Yes	767 (96.6)	27 (3.4)	794 (100.0)	70.11	1	<0.001
	No	2062 (85.6)	347 (14.4)	2409 (100.0)			
Childhood smoking history	No	1603 (87.1)	237 (12.9)	1840 (100.0)	6.04	1	0.014
	Yes	1225 (89.9)	137 (10.1)	1362 (100.0)			
Smokeless tobacco use	No	2078 (88.2)	278 (11.8)	2356 (100.0)	0.12	1	0.725
	Yes	750 (88.7)	96 (11.3)	846 (100.0)			
Substance use	No	2517 (87.3)	365 (12.7)	2882 (100.0)	27.10	1	<0.001

Variable	Category	Without thyroid disease, n (%)	With thyroid disease, n (%)	Total, n (%)	χ^2	df	p-value
Alcohol consumption	Yes	311 (97.2)	9 (2.8)	320 (100.0)	15.98	1	<0.001
	No	2632 (87.7)	368 (12.3)	3000 (100.0)			
	Yes	197 (97.0)	6 (3.0)	203 (100.0)			

Note: Percentages are presented as column percentages within thyroid disease status groups.

3.6. Dietary Micronutrient and Vitamin Intake

Comparison of micronutrient intake using the Mann–Whitney U test showed that mean intake of calcium, iron, magnesium, phosphorus, potassium, sodium, zinc, copper, fluoride, and manganese was significantly higher among participants without thyroid disease than among those with thyroid disease (all $p < 0.05$). Similarly, intake of retinol, vitamin D (both IU and D2/D3 forms), thiamine, riboflavin, niacin, pantothenic acid, folate, and choline was significantly higher in the disease-free group (all $p < 0.05$). No significant between-group differences were observed for vitamin C, vitamin E, vitamin B12, or vitamin K (all $p > 0.05$). Dietary cholesterol intake was also significantly higher among disease-free participants than among those with thyroid disease ($p < 0.001$). Overall, these findings indicate that thyroid disease was associated with lower intake of most essential micronutrients and vitamins in this population.

3.7. Dietary Energy and Macronutrient Intake

Participants with thyroid disease had significantly lower mean intakes of total energy, protein, carbohydrate, total fat, total trans fatty acids, total saturated fatty acids, sucrose, alcohol, and caffeine compared with disease-free participants (all $p < 0.05$). Dietary fiber intake showed a borderline non-significant trend toward lower intake in the thyroid disease group ($p = 0.056$). No significant differences were observed between groups for monounsaturated fatty acid (MUFA, $p = 0.526$) or polyunsaturated fatty acid (PUFA, $p = 0.834$) intake (Table 5).

Table 5. Comparison of Energy and Macronutrient Intake by Thyroid Disease Status (Mann–Whitney U Test)

Variable	Thyroid disease	n	Mean $\pm$ SD	Mean rank	U	Z	p-value
Energy (kcal/day)	Absent	2829	2675.20 $\pm$ 918.93	1632.96	441442	−5.211	<0.001

Variable	Thyroid disease	n	Mean $\pm$ SD	Mean rank	U	Z	p-value
Protein (g/day)	Present	374	2432.47 $\pm$ 762.67	1367.83			
	Absent	2829	85.48 $\pm$ 34.40	1634.56	436908	-5.480	<0.001
Carbohydrate (g/day)	Present	374	76.32 $\pm$ 26.48	1355.70			
	Absent	2829	435.57 $\pm$ 154.07	1636.38	431751	-5.787	<0.001
Total fat (g/day)	Present	374	391.44 $\pm$ 125.64	1341.91			
	Absent	2829	71.31 $\pm$ 28.92	1614.27	494316	-2.065	0.039
Total trans fatty acids (g/day)	Present	374	68.24 $\pm$ 27.41	1509.20			
	Absent	2829	0.267 $\pm$ 0.280	1619.23	480270	-2.901	0.004
Total saturated fatty acids (g/day)	Present	374	0.226 $\pm$ 0.236	1471.64			
	Absent	2829	—	1615.52	490776	-2.276	0.023
MUFA (g/day)	Present	374	—	1499.74			
	Absent	2829	19.14 $\pm$ 9.03	1605.77	518355	-0.635	0.526
PUFA (g/day)	Present	374	18.87 $\pm$ 8.93	1573.48			
	Absent	2829	12.53 $\pm$ 5.83	1600.76	525507	-0.209	0.834
Dietary fiber (g/day)	Present	374	12.56 $\pm$ 5.81	1611.40			
	Absent	2829	29.88 $\pm$ 12.71	1613.34	496943	-1.909	0.056
Sucrose (g/day)	Present	374	28.36 $\pm$ 11.10	1516.22			
	Absent	2829	48.83 $\pm$ 37.11	1624.34	465814	-3.761	<0.001
Alcohol (g/day)	Present	374	42.55 $\pm$ 30.50	1432.99			
	Absent	2829	0.064 $\pm$ 0.127	1623.13	469260	-3.594	<0.001
Caffeine (mg/day)	Present	374	0.047 $\pm$ 0.086	1442.21			
	Absent	2829	160.50 $\pm$ 147.10	1626.95	458428	-4.200	<0.001

Variable	Thyroid disease	n	Mean $\pm$ SD	Mean rank	U	Z	p-value
	Present	374	137.12 $\pm$ 151.06	1413.24			

3.8. Association between Thyroid Disease and Clinical Symptoms and Chronic Comorbidities

Chi-square analysis of clinical symptoms and chronic diseases among the 3,203 participants revealed several significant associations with thyroid disease status. Chronic headache (38.8% vs. 21.6%, $p < 0.001$), memory impairment (8.6% vs. 3.9%, $p < 0.001$), and depression (34.8% vs. 17.7%, $p < 0.001$) were all significantly more prevalent among participants with thyroid disease. Rheumatic disease (5.9% vs. 3.3%, $p = 0.013$), gallstones (7.2% vs. 4.5%, $p = 0.020$), and fatty liver disease (34.2% vs. 19.8%, $p < 0.001$) were also significantly more common in this group. Among metabolic conditions, hypertension (31.8% vs. 23.3%, $p < 0.001$) and diabetes (19.5% vs. 11.6%, $p < 0.001$) were significantly more prevalent among participants with thyroid disease. No significant between-group differences were observed for kidney stones, stroke, myocardial infarction, or cardiac disease (all $p > 0.05$), although the prevalence of kidney stones was marginally higher among participants with thyroid disease (36.6% vs. 31.8%, $p = 0.059$). Overall, thyroid disease was associated with a higher prevalence of psychological symptoms, metabolic disorders, and selected chronic conditions, with the largest between-group differences observed for depression, chronic headache, fatty liver disease, hypertension, and diabetes (Table 6).

Table 6. Distribution and Association of Thyroid Disease with Clinical Symptoms and Chronic Diseases among Participants (N = 3203)

Symptom/Disease	Status	Without thyroid disease, n (%)	With thyroid disease, n (%)	Total, n (%)	χ^2	df	p-value
Chronic headache	Absent	2219 (78.4)	229 (61.2)	2448 (76.4)	54.293	1	<0.001
	Present	610 (21.6)	145 (38.8)	755 (23.6)			
Memory impairment	Absent	2720 (96.1)	342 (91.4)	3062 (95.6)	17.363	1	<0.001
	Present	109 (3.9)	32 (8.6)	141 (4.4)			
Depression	Absent	2329 (82.3)	244 (65.2)	2573 (80.3)	61.027	1	<0.001
	Present	500 (17.7)	130 (34.8)	630 (19.7)			

Symptom/Disease	Status	Without thyroid disease, n (%)	With thyroid disease, n (%)	Total, n (%)	χ^2	df	P-value
Rheumatic disease	Absent	2735 (96.7)	352 (94.1)	3087 (96.4)	6.200	1	0.013
	Present	94 (3.3)	22 (5.9)	116 (3.6)			
Gallstones	Absent	2702 (95.5)	347 (92.8)	3049 (95.2)	5.379	1	0.020
	Present	127 (4.5)	27 (7.2)	154 (4.8)			
Kidney stones	Absent	1930 (68.2)	237 (63.4)	2167 (67.7)	3.555	1	0.059
	Present	899 (31.8)	137 (36.6)	1036 (32.3)			
Chronic pulmonary disease	Absent	2751 (97.2)	359 (96.0)	3110 (97.1)	1.841	1	0.175
	Present	78 (2.8)	15 (4.0)	93 (2.9)			
Fatty liver disease	Absent	2268 (80.2)	246 (65.8)	2514 (78.5)	40.537	1	<0.001
	Present	561 (19.8)	128 (34.2)	689 (21.5)			
Stroke	Absent	2779 (98.2)	362 (96.8)	3141 (98.1)	3.614	1	0.057
	Present	50 (1.8)	12 (3.2)	62 (1.9)			
Myocardial infarction	Absent	2757 (97.5)	362 (96.8)	3119 (97.4)	0.569	1	0.450
	Present	72 (2.5)	12 (3.2)	84 (2.6)			
Cardiac disease	Absent	2576 (91.1)	334 (89.3)	2910 (90.9)	1.220	1	0.269
	Present	253 (8.9)	40 (10.7)	293 (9.1)			
Hypertension	Absent	2170 (76.7)	255 (68.2)	2425 (75.7)	13.051	1	<0.001
	Present	659 (23.3)	119 (31.8)	778 (24.3)			
Diabetes	Absent	2500 (88.4)	301 (80.5)	2801 (87.4)	18.732	1	<0.001
	Present	329 (11.6)	73 (19.5)	402 (12.6)			
Total	—	2829 (100.0)	374 (100.0)	3203			

Symptom/Disease Status	Without thyroid disease, n (%)	With thyroid disease, n (%)	Total, n (%)	χ^2	df	P-value
			(100.0)			

3.9. Multivariable Logistic Regression Analysis of Factors Associated with Thyroid Disease

Variables with $p < 0.25$ in univariate analysis were entered into a multivariable logistic regression model to identify factors independently associated with thyroid disease. Multivariable logistic regression analysis identified several factors independently associated with prevalent thyroid disease. In the final model, sex, history of memory impairment, history of depression, chronic headache, kidney stones, vitamin D intake (IU/day), and total trans fatty acid intake remained independently associated with thyroid disease (Table 7).

Women had approximately 4.6 times higher odds of thyroid disease than men (OR = 4.61; 95% CI: 2.83–7.52; $p < 0.001$), identifying sex as the strongest correlate in the model. Participants with a history of memory impairment had 1.67 times higher odds of thyroid disease (95% CI: 1.05–2.63; $p = 0.029$), and those with a history of depression had 1.47 times higher odds (95% CI: 1.14–1.91; $p = 0.004$). Chronic headache (OR = 1.49; 95% CI: 1.16–1.91; $p = 0.002$) and a history of kidney stones (OR = 1.29; 95% CI: 1.01–1.64; $p = 0.043$) were also independently associated with thyroid disease. Each one-unit increase in vitamin D intake (IU/day) was associated with an 8% increase in the odds of thyroid disease (OR = 1.08; 95% CI: 1.01–1.16; $p = 0.026$), whereas each one-unit increase in total trans fatty acid intake was associated with lower odds of thyroid disease (OR = 0.48; 95% CI: 0.24–0.92; $p = 0.028$). Age (OR = 1.02; 95% CI: 1.00–1.03; $p = 0.059$) and BMI (OR = 1.02; 95% CI: 1.00–1.05; $p = 0.062$) approached, but did not reach, statistical significance (Table 7).

Table 7. Multivariable Logistic Regression Analysis of Factors Independently Associated with Thyroid Disease

Variable	B	SE	Wald	df	p-value	OR (Exp[B])	95% CI for OR
Sex (female vs. male)	1.529	0.249	37.611	1	<0.001	4.61	2.83–7.52
History of memory impairment (yes vs. no)	0.510	0.233	4.784	1	0.029	1.67	1.05–2.63
History of depression (yes vs. no)	0.388	0.133	8.514	1	0.004	1.47	1.14–1.91
Chronic headache (yes vs. no)	0.398	0.128	9.720	1	0.002	1.49	1.16–1.91

Variable	B	SE	Wald	df	p-value	OR (Exp[B])	95% CI for OR
Kidney stones (yes vs. no)	0.251	0.124	4.095	1	0.043	1.29	1.01–1.64
Vitamin D intake (IU/day)	0.080	0.036	4.957	1	0.026	1.08	1.01–1.16
Total trans fatty acid intake (g/day)	–0.744	0.339	4.819	1	0.028	0.48	0.24–0.92
Age (years)	0.016	0.009	3.554	1	0.059	1.02	1.00–1.03
Body mass index (BMI)	0.023	0.012	3.491	1	0.062	1.02	1.00–1.05
Constant	–4.347	0.937	21.526	1	<0.001	0.01	—

Note: Variables with $p < 0.25$ in univariate analysis were entered into the multivariable model. B, unstandardized regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval. Odds ratios for continuous variables represent the change per one-unit increase in the corresponding variable.

4. Discussion

4.1. Summary of Principal Findings

This study, based on the PERSIAN Dena Adult Cohort in southwestern Iran, found a baseline thyroid disease prevalence of 11.7% and a five-year cumulative incidence of 2,261.48 per 100,000 population among participants who were disease-free at enrollment. Female sex was the strongest independent correlate of thyroid disease, and thyroid disease was further associated with lower educational attainment, lower physical activity, a distinct pattern of nutrient intake, and a higher burden of selected psychological, metabolic, and clinical comorbidities, including depression, memory impairment, chronic headache, kidney stones, hypertension, diabetes, and fatty liver disease. Given the large number of variables examined, some observed associations may be attributable to chance, and findings should therefore be interpreted with caution.

4.2. Prevalence and Incidence in Relation to Other Populations

The observed prevalence of 11.7% is broadly consistent with, though somewhat lower than, recent Iranian estimates from Tehran and Isfahan, where prevalence figures of approximately 10–11% and considerably higher figures among older adults in eastern Iran have been reported (6–8), and it falls within the range reported by global reviews of autoimmune and overall thyroid dysfunction (1,3–5). The cumulative incidence identified in this cohort adds prospective evidence from a previously understudied, ethnically Lur, semi-rural population and is broadly

comparable in order of magnitude to incidence figures reported from the iodine-sufficient Isfahan cohort (7), reinforcing the view that, despite Iran's long-standing and well-monitored universal salt iodization program (31,34), thyroid disorders remain a substantial and ongoing public health burden even in regions with adequate iodine status.

4.3. Female Predominance

The associations identified in this study are based on cross-sectional analyses of prevalent thyroid disease and should therefore be interpreted as correlates rather than causal risk factors. The temporal relationship between these variables and thyroid disease cannot be established.

Consistent with the well-documented female predominance of thyroid disorders reported worldwide (1,3–6), women in the present cohort had markedly higher odds of thyroid disease than men. This pattern is thought to reflect the combined influence of sex hormones, X-chromosome-linked immune genes, and sex-specific epigenetic regulation of immune pathways, all of which contribute to a broader female predisposition toward autoimmune disease, including autoimmune thyroiditis (11). The particularly pronounced female-to-male ratio observed in this rural, culturally conservative population may additionally reflect differences in health-seeking behavior, reproductive history, and exposure to hormonal transitions such as pregnancy and menopause, which are recognized windows of vulnerability for the onset of autoimmune thyroid disease (30).

4.4. Physical Activity

Participants with thyroid disease reported significantly lower physical activity levels than their disease-free counterparts. While some large population-based cohorts have found no clear longitudinal association between thyroid hormone levels and physical activity (12), other analyses using nationally representative survey data have identified significant associations between physical activity level and the likelihood of overt and subclinical thyroid dysfunction (12). The cross-sectional nature of the present comparison does not permit a determination of the direction of this association: reduced physical activity could plausibly contribute to metabolic dysregulation predisposing to thyroid dysfunction, or, conversely, symptoms of thyroid disease such as fatigue and reduced exercise tolerance could themselves lead to lower activity levels, a pattern that has been specifically documented among patients with treated hypothyroidism.

4.5. Psychological and Cognitive Correlates

Depression, memory impairment, and chronic headache each emerged as independent correlates of thyroid disease in the multivariable model. The association between hypothyroidism and clinical depression is among the most consistently replicated findings in thyroid epidemiology, with a large meta-analysis reporting an approximately 1.3-fold increased risk of depression across the spectrum of thyroid dysfunction severity (13). Similarly, thyroid hormone dysregulation has been linked to impairments across multiple cognitive domains, particularly

memory and executive function, through effects on cerebral structure, function, and vascular integrity (14). The independent association between chronic headache and thyroid disease observed here is consistent with a growing body of literature describing a bidirectional relationship between migraine, tension-type headache, and hypothyroidism, potentially mediated by shared genetic loci, altered cerebral blood flow, and thyroid hormone effects on central serotonergic and dopaminergic pathways (15).

Collectively, these findings underscore that thyroid disease in this population is not merely a biochemical abnormality but is accompanied by a meaningful burden of psychological and cognitive symptoms that may be under-recognized in routine primary care and that could benefit from validated, disease-specific quality-of-life assessment tools (29).

The observed associations with depression, memory impairment, and chronic headache should be interpreted with caution. These conditions may not represent independent risk factors for thyroid disease but could instead reflect consequences of the disease itself or share common underlying biological or psychosocial mechanisms. Given the cross-sectional nature of most analyses, the temporal direction of these relationships cannot be established, and causal inferences should be avoided.

4.6. Educational Attainment and Socioeconomic Disparities

Thyroid disease prevalence was highest among illiterate participants and those with only primary-level education, and it decreased progressively with higher educational attainment. This pattern parallels findings from other health systems in which socioeconomic status, educational attainment, and health literacy have been identified as key social determinants influencing both the diagnosis and management of thyroid disease (18). In a resource-limited, semi-rural setting such as Dena County, lower educational attainment may act as a proxy for reduced health literacy, delayed care-seeking, and differential access to screening and treatment services, all of which could plausibly translate into a higher observed burden of both undiagnosed and diagnosed thyroid disease among less-educated participants.

The observed association between lower educational attainment and thyroid disease may reflect multiple overlapping mechanisms. In this semi-rural setting, lower education may be linked to reduced healthcare access, lower health literacy, and delays in diagnosis. Additionally, educational attainment is closely related to broader socioeconomic factors that influence dietary patterns, health behaviors, and environmental exposures. Therefore, this association likely reflects a complex interplay of social and structural determinants rather than a direct causal effect of education itself.

4.7. Dietary Patterns: A Complex and Counterintuitive Picture

Participants with thyroid disease reported systematically lower intakes of total energy and most macronutrients and micronutrients compared with disease-free participants. Adequate intake of

iodine, selenium, zinc, iron, and vitamin D is well established as important for normal thyroid hormone synthesis and immune regulation (16,19), and the global pattern of lower micronutrient intake observed in the thyroid disease group is broadly consistent with this literature. However, two specific findings in the multivariable model warrant more cautious interpretation. First, higher vitamin D intake (IU/day) was paradoxically associated with increased, rather than decreased, odds of thyroid disease. Because most randomized and prospective evidence points toward vitamin D deficiency, not sufficiency, as a correlate of autoimmune thyroid disease (16), this counterintuitive finding is more plausibly explained by reverse causation or detection bias for example, participants with a known thyroid diagnosis may be more likely to have been advised by a physician to take vitamin D supplements, or to undergo more frequent laboratory testing that could indirectly reflect greater engagement with the healthcare system rather than by a genuine harmful effect of vitamin D itself.

Second, higher dietary trans fatty acid intake was independently associated with lower odds of thyroid disease. This runs counter to laboratory and small clinical studies suggesting that trans fatty acids can adversely influence thyroid hormone signaling and the $ft3/ft4$ ratio (17). Given that participants with thyroid disease in this cohort also reported systematically lower total energy and macronutrient intake overall, the most parsimonious explanation is that this finding reflects an overall pattern of reduced dietary intake potentially resulting from illness-related changes in appetite, dietary counseling received after diagnosis, or unmeasured confounding by overall food consumption rather than a genuine protective effect of trans fatty acids. This pattern illustrates a broader limitation inherent to cross-sectional dietary comparisons in a prevalent disease population: because dietary intake was assessed at a single time point after disease onset in most prevalent cases, it is not possible to distinguish dietary exposures that preceded and potentially contributed to thyroid disease from dietary changes that occurred as a consequence of the disease or its treatment.

These counterintuitive associations should be interpreted with particular caution in terms of causal inference. Given the predominantly cross-sectional nature of the analyses, the observed relationships are unlikely to reflect true protective or harmful effects. Instead, they are more plausibly explained by reverse causation (e.g., changes in diet or supplement use following diagnosis), residual confounding, and potential detection bias related to differences in healthcare access and utilization. Therefore, these findings should not be interpreted as evidence of causal relationships, and further longitudinal and mechanistic studies are needed to clarify these associations. In addition, because dietary variables were not adjusted for total energy intake, the observed associations may partly reflect differences in overall food consumption rather than specific nutrient effects.

4.8. Cardiometabolic and Hepatic Comorbidities

Hypertension, diabetes, and fatty liver disease were all significantly more prevalent among participants with thyroid disease. These associations align with an extensive literature describing

bidirectional relationships between thyroid dysfunction and cardiometabolic disease: subclinical hypothyroidism has been associated with an increased risk of incident hypertension, particularly among women (21), thyroid dysfunction and type 2 diabetes frequently co-occur and appear to share overlapping pathophysiological mechanisms related to insulin sensitivity and glucose metabolism (22), and a large meta-analysis encompassing nearly 39 million individuals recently confirmed a reciprocal association between hypothyroidism and non-alcoholic fatty liver disease, potentially mediated through shared effects on lipid metabolism, hepatic lipogenesis, and insulin resistance (20). Taken together, these findings reinforce the importance of considering thyroid function as part of a broader cardiometabolic risk assessment in this population, rather than as an isolated endocrine finding.

4.9. Gallstones and Kidney Stones

Both gallstone disease and kidney stones were more prevalent among participants with thyroid disease, and kidney stones remained an independent correlate in the multivariable model. Thyroid hormones are known to influence hepatic cholesterol synthesis, bile composition, and gallbladder motility, with both hypothyroidism and hyperthyroidism capable of promoting cholesterol gallstone formation through distinct molecular mechanisms (27). Similarly, a large NHANES-based analysis found that a history of thyroid disease was independently associated with increased odds of kidney stones even after adjustment for shared metabolic risk factors such as diabetes, hypertension, and gout (25), a finding that may relate to thyroid hormone effects on renal perfusion, calcium handling, and ureteric peristalsis. These associations suggest that clinicians managing patients with thyroid disorders in this population should maintain a heightened awareness of biliary and renal stone disease as potential comorbidities.

4.10. Behavioral Factors: The Smoking and Substance Use Paradox

An unexpected finding was the markedly lower prevalence of thyroid disease among current smokers, substance users, and alcohol consumers compared with non-users. Biologically, this is not entirely implausible: nicotine and thiocyanate exposure from cigarette smoke have well-documented, dose-related effects on thyroid hormone economy and thyroid autoimmunity, generally lowering thyroid-stimulating hormone and thyroid peroxidase antibody titers and thereby potentially reducing the risk of hypothyroidism, even as smoking simultaneously increases the risk of Graves' hyperthyroidism and ophthalmopathy (23,24). However, in this study population, current smoking, substance use, and alcohol consumption were also likely to cluster demographically with younger age and male sex, both of which are independently associated with a lower baseline prevalence of thyroid disease. As such, the apparent protective associations observed here for smoking, substance use, and alcohol consumption most likely reflect substantial residual confounding by sex and age rather than genuine causal protection, and should not be interpreted as supporting these behaviors as protective health strategies, particularly given their well-established harms across numerous other health domains.

4.11. Age, Body Mass Index, and Autoimmune Comorbidity

Age and BMI approached, but did not reach, statistical significance as independent correlates of thyroid disease in the multivariable model. This pattern is broadly in line with previous population-based studies suggesting an association between higher BMI and modest alterations in thyroid function within the euthyroid range (28), although the present findings do not establish a statistically significant relationship.

Although rheumatic disease was more common among participants with thyroid disease in univariate analysis, it did not remain significant after multivariable adjustment. This finding may be consistent with the reported co-occurrence of autoimmune conditions, including autoimmune thyroid disease and rheumatoid arthritis, which have been described to share genetic susceptibility and inflammatory pathways (26). However, given the cross-sectional nature of the data, this observation should be interpreted cautiously and does not imply a causal or clinically actionable relationship.

While certain demographic and clinical characteristics were more common among participants with thyroid disease, these findings should not be interpreted as evidence to support targeted screening or case-finding strategies without further prospective validation.

4.12. Strengths and Limitations

This study benefits from the infrastructure of the PERSIAN Dena Cohort, which provided a large, well-characterized sample drawn from a previously understudied semi-rural population, standardized data collection procedures, and, uniquely among studies from this region, prospective five-year incidence data in addition to baseline prevalence estimates. The availability of detailed dietary, behavioral, and clinical comorbidity data further allowed for a comprehensive multivariable assessment of risk factors.

Several limitations should nonetheless be acknowledged. First, with the exception of the incidence analysis, most associations reported here are cross-sectional and cannot establish temporal or causal relationships; this is particularly relevant to the counterintuitive dietary findings discussed above, which are more likely explained by reverse causation than by a true causal effect of diet on thyroid disease risk. Second, thyroid disease status was based on self-reported physician diagnosis and medication use rather than on directly measured thyroid function tests (e.g., serum TSH and free T4) for the entire cohort. This approach may have led to under-detection of subclinical thyroid dysfunction, which is more common than overt disease, introduced misclassification bias, and may have partially reflected differences in healthcare access and diagnosis rather than the true underlying disease burden. Therefore, the reported prevalence and incidence should be interpreted as reflecting clinically diagnosed or treated thyroid disease, and may underestimate the true burden of thyroid dysfunction, particularly subclinical disease. Third, the fifth year of the incidence analysis was based on incomplete

follow-up and likely underestimates the true annual incidence for that year. Fourth, as with any single-region cohort, the generalizability of these findings to other Iranian provinces or to other countries with different genetic backgrounds, iodine intake patterns, and healthcare systems may be limited. Fifth, although the multivariable model adjusted for a substantial number of covariates, residual confounding particularly by unmeasured genetic susceptibility, autoantibody status, and detailed reproductive history in women cannot be excluded. Sixth, thyroid disease was analyzed as a composite outcome encompassing a heterogeneous group of conditions, including hypothyroidism, hyperthyroidism, autoimmune thyroiditis, goiter, and thyroid nodules. These conditions have distinct pathophysiological mechanisms and risk factor profiles; therefore, the observed associations may not be uniform across specific thyroid disorders, and combining them into a single category may obscure condition-specific relationships. Future studies with more detailed phenotyping are needed to disentangle these differences. Seventh, detailed micronutrient-specific analyses were not among the primary objectives of this study. Therefore, micronutrient intake variables were not comprehensively reported, and the dietary findings should be interpreted within the broader context of overall dietary patterns. Eighth, the large number of statistical comparisons performed increases the possibility of type I error (false-positive findings).

4.13. Public Health and Clinical Implications

Iran's universal salt iodization program has achieved and sustained the elimination of iodine deficiency disorders at the national level for over two decades (31,34), yet the substantial burden of thyroid disease identified in this cohort indicates that iodine sufficiency alone has not eliminated the broader public health impact of thyroid disorders, particularly in a population with a high burden of female-predominant, low-education, and multimorbid participants. While general population screening for asymptomatic thyroid dysfunction is not currently recommended by major preventive health task forces given the lack of demonstrated benefit on clinical outcomes (33), the markedly higher prevalence and distinct sociodemographic and clinical risk profile identified in this study suggest that a more targeted, risk-based case-finding approach focused on women, individuals with lower educational attainment, and those with comorbid depression, chronic headache, or metabolic disease may be a more efficient strategy for this population than either universal screening or a purely symptom-triggered approach. Such an approach would also be consistent with broader primordial and primary prevention strategies for thyroid disease that have been proposed at the national level in Iran (32).

5. Conclusion

In this prospective cohort study from southwestern Iran, thyroid disease affected approximately one in nine adults at baseline, with a five-year cumulative incidence of 2,261.48 per 100,000 among initially disease-free participants. Female sex was the strongest independent correlate of thyroid disease, and several demographic, behavioral, and clinical characteristics were more common among affected individuals.

These findings indicate that clinically diagnosed thyroid disease is relatively common in this population and that certain subgroups have a higher prevalence. However, the observed associations are based primarily on cross-sectional analyses and may reflect disease consequences, healthcare utilization patterns, or residual confounding rather than causal relationships.

Accordingly, these results should not be interpreted as supporting targeted screening or case-finding strategies without further prospective validation. Instead, they provide descriptive epidemiological insights that may help inform the design of future longitudinal and interventional studies.

Declarations

Ethics approval and consent to participate: This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the national guidelines for research ethics. Ethical approval was obtained from the Ethics Committee of Yasuj University of Medical Sciences (Approval ID: IR.YUMS.REC.1404.205). The study was also conducted in alignment with the regulations and framework of the PERSIAN Cohort Study. Written informed consent was obtained from all participants prior to enrollment. As the PERSIAN Dena Cohort Study includes only adults aged 35–70 years, no participants under the age of 16 years were included in this study.

Consent for publication: Not applicable.

Availability of data and materials: The datasets generated and/or analyzed during the current study are not publicly available due to confidentiality agreements but are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: This study was supported by Yasuj University of Medical Sciences. The funding body had no role in the design of the study; collection, analysis, and interpretation of data; or in writing the manuscript.

Authors' contributions: M.M.J., M.N., and S.S. contributed to the study conception and design. Data collection was performed by M.M.J., M.R. and M.S.N. Statistical analysis was conducted by M.M.J., M.R. and M.N. The first draft of the manuscript was written by M.M.J., M.N., M.S.N. and S.S., and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgements: The authors would like to express their sincere gratitude to the staff of the DENA Cohort Center and the PERSIAN Cohort Study headquarters for their continuous support

and collaboration in data collection and management. We also thank all study participants for their valuable time and commitment to this research.

References

1. Zhang X, Wang X, Hu H, Qu H, Xu Y, Li Q. Prevalence and trends of thyroid disease among adults, 1999-2018. *Endocr Pract.* 2023;29(11):875-880.
2. Baretella O, Blum MR, Abolhassani N, Alwan H, Wildisen L, Del Giovane C, et al. Associations between subclinical thyroid dysfunction and cardiovascular risk factors according to age and sex. *J Clin Endocrinol Metab.* 2024;dgae860.
3. Hu X, Chen Y, Shen Y, Tian R, Sheng Y, Que H. Global prevalence and epidemiological trends of Hashimoto's thyroiditis in adults: a systematic review and meta-analysis. *Front Public Health.* 2022;10:1020709.
4. Mu C, Ming X, Tian Y, Liu Y, Yao M, Ni Y, et al. Mapping global epidemiology of thyroid nodules among general population: a systematic review and meta-analysis. *Front Oncol.* 2022;12:1029926.
5. Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F, Galofré JC. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. *J Clin Endocrinol Metab.* 2014;99(3):923-931.
6. Ghaemmaghami Z, Firoozbakhsh P, Gholami D, Khodabandelu S, Baay M, Alemzadeh-Ansari MJ, et al. Increased prevalence of thyroid dysfunction in Tehran – HAMRAH study. *BMC Endocr Disord.* 2023;23(1):270.
7. Aminorroaya A, Meamar R, Amini M, Feizi A, Tabatabae A, Faghih Imani E. Incidence of thyroid dysfunction in an Iranian adult population: the predictor role of thyroid autoantibodies: results from a prospective population-based cohort study. *Eur J Med Res.* 2017;22(1):21.
8. Mirahmad M, Mansour A, Moodi M, Safkhani E, Haghpanah V, Asili P, et al. Prevalence of thyroid dysfunction among Iranian older adults: a cross-sectional study. *Sci Rep.* 2023;13:21651.
9. Poustchi H, Egtesad S, Kamangar F, Etemadi A, Keshtkar AA, Hekmatdoost A, et al. Prospective epidemiological research studies in Iran (the PERSIAN Cohort Study): rationale, objectives, and design. *Am J Epidemiol.* 2018;187(4):647-655.
10. Harooni J, Joukar F, Goujani R, Khalighi Sikaroudi M, Hatami A, Zolghadrpour MA, et al. Cohort profile: the PERSIAN Dena Cohort Study (PDCS) of non-communicable diseases in Southwest Iran. *BMJ Open.* 2024;14(4):e079697.

11. Fairweather D, Beetler DJ, McCabe EJ, Lieberman SM. Mechanisms underlying sex differences in autoimmunity. *J Clin Invest*. 2024;134(18):e180076.
12. Tian L, Lu C, Teng W. Association between physical activity and thyroid function in American adults: a survey from the NHANES database. *BMC Public Health*. 2024;24:1277.
13. Bode H, Ivens B, Bschor T, Schwarzer G, Henssler J, Baethge C. Association of hypothyroidism and clinical depression: a systematic review and meta-analysis. *JAMA Psychiatry*. 2021;78(12):1375-1383.
14. Eslami-Amirabadi M, Sajjadi SA. The relation between thyroid dysregulation and impaired cognition/behaviour: an integrative review. *J Neuroendocrinol*. 2021;33(3):e12948.
15. Tasnim S, Nyholt DR. Migraine and thyroid dysfunction: co-occurrence, shared genes and biological mechanisms. *Eur J Neurol*. 2023;30(6):1815-1827.
16. Taheriniya S, Arab A, Hadi A, Fadel A, Askari G. Vitamin D and thyroid disorders: a systematic review and meta-analysis of observational studies. *BMC Endocr Disord*. 2021;21(1):171.
17. Wang X, Jiang F, Chen W, Yuan H, Li Y. The association between circulating trans fatty acids and thyroid function measures in U.S. adults. *Front Endocrinol (Lausanne)*. 2022;13:928730.
18. Chen DW, Singh Ospina N, Haymart MR. Social determinants of health and disparities in thyroid care. *J Clin Endocrinol Metab*. 2024;109(3):e1309-e1313.
19. Shulhai AM, Rotondo R, Petraroli M, Patianna V, Predieri B, Iughetti L, Esposito S, Street ME. The role of nutrition on thyroid function. *Nutrients*. 2024;16(15):2496.
20. Ayati Firoozabadi A, Elahi Vahed I, Lotfi P, Geshani A, Keshavarzian A, Moftakhar M, et al. The reciprocal relationship between non-alcoholic fatty liver disease and hypothyroidism: a systematic review and meta-analysis of about 39 million individuals. *PLoS One*. 2025;20(12):e0338413.
21. Kim J, Prasitlumkum N, Randhawa S, Banerjee D. Association between subclinical hypothyroidism and incident hypertension in women: a systematic review and meta-analysis. *J Clin Med*. 2021;10(15):3318.
22. Hadgu R, Worede A, Ambachew S. Prevalence of thyroid dysfunction and associated factors among adult type 2 diabetes mellitus patients, 2000–2022: a systematic review and meta-analysis. *Syst Rev*. 2024;13:119.
23. Gruppen EG, Kootstra-Ros J, Muller Kobold A, Connelly MA, Touw D, Bos JHJ, Hak E, Links TP, Bakker SJL, Dullaart RPF. Cigarette smoking is associated with higher thyroid hormone and lower TSH levels: the PREVEND study. *Endocrine*. 2020;67(3):613-622.

24. Liu J, Feng Z, Gao R, Liu P, Meng F, Fan L, Liu L, Du Y. Analysis of risk factors for autoimmune thyroid disease based on blood indicators and urinary iodine concentrations. *Front Endocrinol (Lausanne)*. 2024;15:1453828.
25. Xue W, Xue Z, Liu Y, Yin P, Liu L, Qu S, Wu S, Yang C. Is kidney stone associated with thyroid disease? The United States National Health and Nutrition Examination Survey 2007-2018. *Endocr Metab Immune Disord Drug Targets*. 2024;24(11):1323-1334.
26. Lichtiger A, Fadaei G, Tagoe CE. Autoimmune thyroid disease and rheumatoid arthritis: where the twain meet. *Clin Rheumatol*. 2024;43(3):895-905.
27. Ravi PC, Thugu TR, Singh J, Dasireddy RR, Kumar SA, Isaac NV, Oladimeji A, DeTrollo V, Abdalla R, Mohan V, Iqbal J. Gallstone disease and its correlation with thyroid disorders: a narrative review. *Cureus*. 2023;15(9):e45116.
28. Diniz MFHS, Beleigoli AMR, Bensenor IM, Lotufo PA, Goulart AC, Barreto SM. Association between TSH levels within the reference range and adiposity markers at the baseline of the ELSA-Brasil study. *PLoS One*. 2020;15(2):e0228801.
29. Uslar V, Becker C, Weyhe D, Tabriz N. Thyroid disease-specific quality of life questionnaires – a systematic review. *Endocrinol Diab Metab*. 2022;5(5):e357.
30. Frank-Raue K, Raue F. Thyroid dysfunction in peri- and postmenopausal women – cumulative risks. *Dtsch Arztebl Int*. 2023;120(18):311-316.
31. Delshad H, Mirmiran P, Abdollahi Z, Salehi F, Azizi F. Continuously sustained elimination of iodine deficiency: a quarter of a century success in the Islamic Republic of Iran. *J Endocrinol Invest*. 2018;41(9):1089-1095.
32. Azizi F, Mehran L, Hosseinpanah F, Delshad H, Amouzegar A. Primordial and primary preventions of thyroid disease. *Int J Endocrinol Metab*. 2017;15(4):e57871.
33. Birtwhistle R, Morissette K, Dickinson JA, Reynolds DL, Avey MT, Reyes Domingo F, Rodin R, Thombs BD; Canadian Task Force on Preventive Health Care. Recommendation on screening adults for asymptomatic thyroid dysfunction in primary care. *CMAJ*. 2019;191(46):E1274-E1280.
34. Mohammadi M, Azizi F, Hedayati M. Iodine deficiency status in the WHO Eastern Mediterranean Region: a systematic review. *Environ Geochem Health*. 2018;40(1):87-97.