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Prevalence and risk factors of hypothyroidism after universal salt iodisation: a large cross-sectional study from 31 provinces of China

Jiashu Li,[1] Yongze Li ,[1] Xiaoguang Shi,[2] Di Teng,[1] Xiaochun Teng,[1] Weiping Teng,[1] Zhongyan Shan ,[1] Thyroid Disorders, Iodine Status and Diabetes Epidemiological Survey Group

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[1]Department of Endocrinology and Metabolism, Institute of Endocrinology, NHC Key Laboratory of Diagnosis and Treatment of Thyroid Diseases, The First Hospital of China Medical University, Shenyang, Liaoning, China
[2]Department of Endocrinology, Shengjing Hospital of China Medical University, Shenyang, China

Correspondence to
Professor Zhongyan Shan; shanzhongyan@medmail.com.cn

ABSTRACT

Objectives To investigate the prevalence and risk factors of hypothyroidism after universal salt iodisation for 20 years in mainland China.

Design Nationwide, cross-sectional survey.

Setting and participants The Thyroid Disorders, Iodine Status and Diabetes epidemiological study included adults from 31 provinces of China. Data included demographic, physical characteristics, urine, serum thyroid-stimulating hormone (TSH), thyroid-peroxidase antibody (TPOAb), thyroglobulin antibody (TgAb) and thyroid ultrasonography. Subclinical hypothyroidism (SCH) was classified into severe SCH (TSH >10 mU/L) and mild SCH (TSH 4.2–9.9 mU/L). A total of 78 470 (38 182 men and 40 288 women) participants were included in the final analysis.

Results The prevalence of hypothyroidism was 13.95%. The prevalence rates of overt hypothyroidism (OH) and SCH were 1.02% and 13.93%, which mild SCH was significantly higher than severe SCH (12.18% vs 0.75%). Prevalence was higher in women than in men, and this gender difference was noted among all age groups. The prevalence of mild SCH, severe SCH and OH increases by 1.16%, 1.40% and 1.29% for every 10 years older. TPOAb or/and TgAb positive were significantly associated with OH and severe SCH (OR 15.9, p<0.001). However, SCH was positively correlated with increased urine iodine concentration, but this correlation was only in antibody-negative female patients. In non-autoimmune and male populations, there was a U-shaped relationship between severe SCH and OH and urine iodine concentration.

Conclusions Mild SCH is the most common form of hypothyroidism, which is related to iodine intake. Severe SCH is more similar to OH which autoimmune is the main cause. The various effects of iodine on hypothyroidism depend on thyroid autoimmune and gender.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A sample size of 78 470 individuals was selected, with random selection at urban and rural locations; and there was representation from all 31 provinces of China.
⇒ The study reported the prevalence of mild subclinical hypothyroidism (SCH), severe SCH and overt hypothyroidism and their associated factors using recent data.
⇒ This large sample size, covering a wide area study could not rule out genetic or environmental factors that may have affected the results.
⇒ This cross-sectional study cannot establish causal association between iodine nutritional status and prevalence of hypothyroidism.
⇒ This study was an epidemiological investigation and cannot be repeated thyroid-stimulating hormone testing like the clinical diagnosis of SCH.

INTRODUCTION

Overt hypothyroidism (OH) and subclinical hypothyroidism (SCH) can be associated with hypercholesterolemia, atherosclerosis, all-cause death, infertility and adverse pregnancy outcomes.[1–3] Hypothyroidism is a common disease, which is divided into OH and SCH. SCH is further classified into mild SCH and severe SCH based on serum thyroid-stimulating hormone (TSH) level. Previous studies have found the prevalence of OH to range between 0.3 and 5.3%[4–8] and the prevalence of SCH to range between 0.9% and 16.7%.[6 9] The variation in rate could be due to differences in disease definition, reference ranges, serum thyroid hormone testing techniques, genetic background, age, gender and iodine nutritional status. In a 1995 survey[6] of 25 862 American adults using a TSH cut-off of 5.1 mU/L, the prevalence of OH was 0.4%, and the prevalence of SCH was 9%. In the 1988–1994 US NHANES III Study[8] of 17 353 people over the age of 12 using a TSH cut-off of 4.5 mU/L, the total prevalence of hypothyroidism was 4.6%; and of this, 0.3% was OH and 4.3% was SCH. In 1998, Laurberg *et al*[10] found that the prevalence of SCH in Iceland, with a high iodine intake, was about four times that of Denmark, with a lower

iodine intake. Our previous prospective study in three different levels of iodine intake in China found that the prevalence and incidence of hypothyroidism increased in areas with excess iodine intake.[11 12] The prevalence of hypothyroidism was affected by different populations,[13 14] different TSH cut-off values[4 6–8 15] and different iodine nutritional status.

In 1995, the median urinary iodine level of Chinese residents was 164.8 µg/L, but the prevalence of goitre among school-age children remained at 7%. Mandatory universal salt iodisation (USI) was, thus, introduced nationwide in 1996. China has undergone USI for 20 years since 1996, the Chinese population underwent a series of changes in iodine nutrition.[16] From the survey of thyroid diseases in mainland China, it can be seen that the prevalence of hypothyroidism is gradually increasing, and SCH is more obvious. The prevalence of OH in 1999, 2007, 2010 and 2016 was 1.04%, 0.24%, 1.10% and 1.02%, the prevalence of SCH was 3.22%, 3.51%, 16.70% and 12.93%. The objective of the study was to evaluate the current prevalence of hypothyroidism, analyse the risk factors related to hypothyroidism and provide reasonable preventive measures for hypothyroidism.

MATERIALS AND METHODS

Study participants

The Thyroid Disorders, Iodine Status and Diabetes epidemiological study was based on a representative sample population from a nationwide epidemiological survey conducted in 31 provinces in China between 2015 and 2017,[16] aimed to re-evaluate the current situation of iodine nutrition and the prevalence of thyroid disorders as well as the relationships between them. This study used a whole-group stratified random sampling method. There were four stages: in the first stage, 10 developed cities, 13 developing cities and 8 backward cities were selected nationwide according to the population size and economic level of the cities, for a total of 31 city sites covering 31 provinces nationwide; in the second stage, one municipal district was randomly selected in each city; in the third stage, two residential neighbourhoods were randomly selected in each municipal district; in the fourth stage, according to the inclusion criteria and age-sex stratification. In the fourth stage, a random sample of qualified survey respondents was selected from residential communities according to the inclusion criteria and age–sex stratification. The age, gender, and urban–rural population ratios for each area were calculated based on the 2010 Chinese census data. The sampling method for rural areas is the same as the urban sampling method above.[16] The inclusion criteria for the present study were: aged 18 years and older; having taken no iodine-containing drugs or contrast agents within the past 3 months; non-pregnant women.

The questionnaire included demographic information, a personal and family history of thyroid disease, smoking status, household income, education levels and consumption of household salt. Samples of urine and blood were obtained from each participant in the morning after an overnight fast. The blood specimens were centrifuged, separated and preserved at −20°C before further processing. All specimens were sent to the Shenyang Central Laboratory by a cold chain air transport system in 1 month for centralised testing.

All subjects underwent a thyroid ultrasound, performed by qualified observers, who had trained and passed examination in the project centre. The ultrasound instrument was a portable LOGIQ 100 PRO (GE, Milwaukee, Wisconsin) with 7.5 MHz linear transducers.

Patient and public involvement

There was no patient or public involvement in the development and design of this study.

Laboratory tests

Serum TSH, thyroid-peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) were measured via an electrochemiluminescence immunoassay using a Cobas Elecsys 601 (Roche Diagnostics, Switzerland). Free thyroxin (FT_4) and free tiiodothyronine (FT_3) levels were measured only if TSH was outside the reference range. The intra-assay coefficients of variation (CVs) for serum FT_4, FT_3, TSH, TPOAb and TgAb were 1.1%–6.3%. The inter-assay CVs were 1.9%–9.5%. There were standard operating procedures for serum and urine collection process, time points for testing. External quality assessment materials were used to evaluate external quality control measures. The reference ranges for TSH, FT_4, FT_3, TPOAb and TgAb were 0.27–4.20 mU/L, 12.0–22.0 pmol/L, 3.1–6.8 pmol/L, 0–34 IU/mL and 0–115 IU/mL, respectively, provided by the test kit manufacturers.

Urine iodine was measured via inductively coupled plasma mass spectrometry using an Agilent 7700x (Agilent Technologies, Agilent Technologies, USA). The measurement quality was controlled against certified reference materials (GBW09108, GBW9109 and GBW9110) from the Center for Disease Control in China. The target values of the standards were 70.8±9.0 µg/L, 143±10 µg/L and 224±14 µg/L; with interassay CVs of 2.3%, 2.5% and 2.4% respectively, and intra-assay CVs of 2.7%, 1.4% and 2.3%, respectively.

Diagnosis criterion

Thyroid dysfunction was defined as follows: OH: TSH >4.2 mU/L; FT4 <12 pmol/L. SCH: TSH >4.2 mU/L; FT4 between 12–22 pmol/L. mild SCH: TSH between >4.2–9.9 mU/L; FT4 between 12–22 pmol/L. severe SCH: TSH ≥10 mU/L; FT4 between 12–22 pmol/L.[17] Autoimmune thyroiditis (AIT): TPOAb>34 IU/mL or TgAb>115 IU/mL.

Statistical analysis

To ensure that results applied to the national population, all data were weighted using coefficients from the 2010 China Census data and sampling methods. SE data obtained through complex sampling were obtained using

Table 1 Characteristics of study participants

Variables	Euthyroid	Mild SCH	Severe SCH	OH	P for trend	Euthyroid	Mild SCH	Severe SCH	OH	P for trend
	Men (N=38 182)					Women (N=40 288)				
Number of participants	31 816 (83.3)	3964 (10.4)	274 (0.7)	226 (0.6)	–	28 530 (70.8)	6399 (15.9)	472 (1.2)	715 (1.8)	–
Mean age, years	42.4 (0.1)	46.0 (0.3)	53.5 (1.0)	54.2 (1.1)	<0.001	42.7 (0.1)	46.3 (0.2)	49.6 (0.7)	49.7 (0.5)	<0.001
Education level										
Primary school and lower	4965 (15.7)	828 (21.0)	92 (33.7)	81 (36.2)	<0.001	7104 (25.0)	1937 (30.4)	180 (38.2)	298 (41.8)	<0.001
Middle and high school	15 786 (49.8)	1891 (47.9)	118 (43.2)	99 (44.2)	–	12 316 (43.3)	2693 (42.3)	191 (40.6)	297 (41.7)	–
College and higher	10 964 (34.6)	1228 (31.1)	63 (23.1)	44 (19.6)	–	9012 (31.7)	1740 (27.3)	100 (21.2)	118 (16.5)	–
Iodine intake										
Adequate iodine intake	16 145 (50.7)	1734 (43.7)	100 (36.5)	108 (47.8)	<0.001	14 747 (51.7)	2804 (43.8)	178 (37.7)	367 (51.3)	<0.001
More than adequate iodine intake	11 684 (36.7)	1521 (38.4)	109 (39.8)	94 (41.6)	–	10 417 (36.5)	2511 (39.2)	204 (43.2)	272 (38.0)	–
Excessive iodine intake	3987 (12.5)	709 (17.9)	65 (23.7)	24 (10.6)	–	3366 (11.8)	1084 (16.9)	90 (19.1)	76 (10.6)	–
Percentage consumption of iodised salt	30 483 (95.8)	3807 (96.0)	264 (96.4)	217 (96.0)	0.05	27 169 (95.2)	6148 (96.1)	451 (95.6)	677 (94.7)	0.03
Coastal residents	9369 (29.4)	850 (21.4)	43 (15.7)	52 (23.0)	<0.001	8229 (28.8)	1373 (21.5)	93 (19.7)	153 (21.4)	<0.001
Urban residents	16 877 (53.0)	2015 (50.8)	143 (52.2)	100 (44.2)	0.004	15 096 (52.9)	3463 (54.1)	231 (48.9)	340 (47.6)	0.002
Race										
Han	28 741 (90.3)	3512 (88.6)	225 (82.1)	182 (80.5)	<0.001	25 282 (88.6)	5653 (88.3)	387 (82.0)	574 (80.3)	<0.001
Tibetan	678 (2.1)	132 (3.3)	21 (7.7)	11 (4.9)	–	983 (3.5)	305 (4.8)	39 (8.3)	56 (7.8)	–
Uighur	879 (2.8)	69 (1.7)	8 (2.9)	11 (4.9)	–	890 (3.1)	150 (2.3)	16 (3.4)	32 (4.5)	–
Hui	594 (1.9)	200 (5.1)	17 (6.2)	14 (6.2)	–	560 (2.0)	205 (3.2)	13 (2.8)	30 (4.2)	–
Zhuang	924 (2.9)	51 (1.29)	3 (1.09)	8 (3.54)	–	815 (2.9)	86 (1.3)	17 (3.6)	23 (3.2)	–
Income per year, yuan										
<10000	5726 (18.2)	867 (22.2)	56 (20.7)	74 (33.3)	0.14	6590 (23.4)	1575 (25.0)	132 (28.4)	223 (31.5)	0.008
10000–30000	6516 (20.7)	847 (21.7)	68 (25.2)	57 (25.7)	–	6600 (23.5)	1539 (24.4)	104 (22.4)	184 (26.0)	–
>30000	19 210 (61.1)	2198 (56.2)	146 (54.1)	91 (41.0)	–	14 949 (53.1)	3185 (50.6)	229 (49.3)	301 (42.5)	–
Cigarette smoking										
Never smoked	15 224 (47.9)	2298 (58.1)	164 (59.9)	114 (50.4)	<0.001	27 594 (96.8)	6212 (97.2)	456 (96.8)	686 (96.2)	0.17
Smoker	16 585 (52.1)	1660 (41.9)	110 (40.1)	112 (49.6)	–	922 (3.2)	176 (2.8)	15 (3.2)	27 (3.8)	–
Family history of thyroid disease	1301 (4.1)	131 (3.3)	10 (3.7)	16 (7.2)	0.011	1626 (5.7)	440 (6.9)	35 (7.5)	76 (10.7)	<0.001

Continued

Table 1 Continued

Variables	Euthyroid	Mild SCH	Severe SCH	OH	P for trend	Euthyroid	Mild SCH	Severe SCH	OH	P for trend
	Men (N=38 182)					Women (N=40 288)				
Mean body mass index, kg/m^2	24.5 (0.02)	24.7 (0.06)	24.7 (0.22)	25.3 (0.27)	<0.001	23.35 (0.2)	23.8 (0.05)	24.2 (0.2)	24.9 (0.1)	<0.001
Mean UIC, µg/L	252.1 (4.3)	321.3 (28.2)	280.7 (32.1)	282.4 (27.0)	<0.001	244.3 (3.6)	277.9 (15.5)	427.6 (133.7)	221.2 (12.2)	<0.001
Mean TPOAb, IU/mL	17.19 (0.3)	41.57 (1.7)	115.66 (11.7)	161.01 (14.9)	<0.001	28.2 (0.4)	64.9 (1.7)	159.0 (9.6)	202.5 (8.6)	<0.001
Mean TgAb, IU/mL	30.48 (0.8)	79.96 (5.3)	330.58 (54.3)	407.73 (60.8)	<0.001	67.1 (1.4)	143.4 (5.4)	381.7 (39.7)	505.6 (36.0)	<0.001
Median TSH, mIU/L	2.0 (1.5, 2.7)	5.2 (4.6, 6.3)	12.3 (11.0, 16.1)	10.6 (6.3, 38.5)	<0.001	2.2 (1.6, 2.9)	5.3 (4.7, 6.4)	12.4 (10.9, 15.4)	9.8 (5.9, 27.0)	<0.001
Median FT_4, pmol/L	17.0 (15.3, 19.0)	16.5 (14.9, 18.1)	14.9 (13.6, 16.4)	10.8 (8.6, 11.5)	<0.001	16.0 (14.6, 17.6)	15.6 (14.1, 16.9)	14.0 (12.9, 15.4)	10.8 (9.2, 11.6)	<0.001
Echogenicity										
Hypoechogenicity	381 (1.3)	130 (3.5)	22 (8.4)	28 (12.7)	<0.001	732 (2.7)	418 (6.9)	57 (12.3)	141 (20.4)	<0.001
Isoechogenicity	25 997 (87.8)	3072 (82.7)	168 (64.1)	125 (56.6)	–	22 800 (85.4)	4636 (76.7)	283 (61.3)	329 (47.5)	–
Hyperechogenicity	1363 (4.6)	80 (2.2)	3 (1.1)	5 (2.3)	–	712 (2.7)	61 (1.0)	6 (1.3)	9 (1.3)	–
Heterogeneous echogenicity	1872 (6.3)	433 (11.7)	69 (26.3)	63 (28.5)	–	2457 (9.2)	929 (15.4)	116 (25.1)	213 (30.8)	–
Diffuse goitre	0 (0.0)	16 (0.4)	5 (1.8)	1 (0.4)	<0.001	0 (0.0)	42 (0.7)	13 (2.8)	34 (4.8)	<0.001
Nodular goitre	0 (0.0)	16 (0.4)	3 (1.1)	1 (0.4)	<0.001	0 (0.0)	43 (0.7)	7 (1.5)	22 (3.1)	<0.001

Data are weighted and expressed as number (%), mean (SE) or median (quartile).

OH, overt hypothyroidism; SCH, subclinical hypothyroidism; TgAb, thyroglobulin antibody; TPOAb, thyroid-peroxidase antibody; UIC, urinary iodine concentration.

Table 2 Age-standardised and gender-standardised prevalence of mild SCH, severe SCH and OH in the general Chinese adult population

	Prevalence % of mild SCH (95% CI)			Prevalence % of severe SCH (95% CI)			Prevalence % of OH (95% CI)		
	Men	Women	Total	Men	Women	Total	Men	Women	Total
N	3964	6399	10363	274	472	746	226	715	941
Prevalence	9.30 (8.57 to 10.09)	15.12 (14.03 to 16.27)	12.18 (11.31 to 13.10)	0.56 (0.43 to 0.74)	0.94 (0.82 to 1.08)	0.75 (0.65 to 0.87)	0.53 (0.41 to 0.67)	1.53 (1.33 to 1.75)	1.02 (0.88 to 1.18)
Age									
18–29	8.74 (7.81 to 9.76)	13.58 (12.14 to 15.17)	11.14 (10.23 to 12.11)	0.59 (0.26 to 1.34)	0.67 (0.51 to 0.89)	0.63 (0.41 to 0.97)	0.13 (0.06 to 0.31)	0.77 (0.41 to 1.44)	0.45 (0.25 to 0.80)
30–39	7.08 (6.34 to 7.89)	12.22 (11.24 to 13.27)	9.59 (8.82 to 10.43)	0.36 (0.21 to 0.61)	0.66 (0.52 to 0.84)	0.50 (0.39 to 0.66)	0.31 (0.19 to 0.50)	1.11 (0.84 to 1.48)	0.70 (0.55 to 0.89)
40–49	8.32 (7.28 to 9.49)	14.67 (12.76 to 16.81)	11.43 (10.06 to 12.96)	0.29 (0.21 to 0.40)	0.94 (0.72 to 1.24)	0.61 (0.48 to 0.78)	0.51 (0.39 to 0.67)	2.05 (1.64 to 2.55)	1.26 (1.04 to 1.53)
50–59	10.15 (9.05 to 11.37)	17.87 (15.93 to 19.98)	13.94 (12.67 to 15.43)	0.82 (0.56 to 1.21)	1.31 (0.99 to 1.73)	1.06 (0.83 to 1.36)	0.71 (0.41 to 1.23)	1.93 (1.52 to 2.44)	1.31 (1.00 to 1.72)
≥60	13.54 (11.84 to 15.45)	18.94 (16.96 to 21.10)	16.30 (14.58 to 18.17)	0.90 (0.63 to 1.29)	1.35 (1.05 to 1.75)	1.13 (0.88 to 1.45)	1.28 (0.99 to 1.64)	2.12 (1.73 to 2.61)	1.71 (1.40 to 2.09)
P for trend	0.60	0.002	0.16	0.32	0.07	0.47	<0.001	0.02	<0.001
BMI (kg/m^2)									
<18.5	4.25 (3.00 to 6.00)	7.30 (6.51 to 8.17)	11.55 (9.8 to 13.56)	0.56 (0.16 to 1.91)	0.44 (0.20 to 0.95)	0.99 (0.37 to 2.67)	0.23 (0.09 to 0.56)	0.35 (0.21 to 0.61)	0.58 (0.36 to 0.93)
18.5–24.9	4.51 (4.05 to 5.02)	7.44 (6.89 to 8.03)	11.96 (11.01 to 12.98)	0.23 (0.18 to 0.30)	0.44 (0.38 to 0.51)	0.67 (0.58 to 0.78)	0.23 (0.18 to 0.30)	0.68 (0.57 to 0.81)	0.91 (0.78 to 1.07)
≥25	4.97 (4.60 to 5.37)	7.89 (6.95 to 8.95)	12.86 (11.71 to 14.11)	0.27 (0.21 to 0.35)	0.61 (0.47 to 0.78)	0.88 (0.74 to 1.05)	0.29 (0.22 to 0.40)	0.92 (0.77 to 1.09)	1.21 (1.02 to 1.43)
P for trend	0.60	0.002	0.16	0.32	0.07	0.47	<0.001	0.02	<0.001
Income per year, yuan									
<10 000	5.09 (4.45 to 5.81)	7.8 (6.95 to 8.75)	12.89 (11.56 to 14.34)	0.18 (0.12 to 0.25)	0.52 (0.42 to 0.65)	0.70 (0.56 to 0.87)	0.34 (0.21 to 0.54)	0.89 (0.71 to 1.11)	1.23 (0.97 to 1.57)
10 000–30000	4.77 (4.11 to 5.52)	7.77 (7.19 to 8.39)	12.54 (11.62 to 13.51)	0.3 (0.21 to 0.43)	0.47 (0.37 to 0.60)	0.77 (0.64 to 0.92)	0.27 (0.16 to 0.47)	0.73 (0.59 to 0.90)	1.00 (0.79 to 1.28)
>30 000	4.60 (4.18 to 5.06)	7.25 (6.56 to 8.01)	11.85 (10.86 to 12.92)	0.32 (0.22 to 0.45)	0.45 (0.37 to 0.56)	0.77 (0.60 to 0.98)	0.24 (0.18 to 0.31)	0.71 (0.58 to 0.88)	0.95 (0.8 to 1.13)
P for trend	0.02	0.006	<0.001	0.21	0.02	0.35	0.03	0.048	0.003
Location									
Urban	4.57 (3.99 to 5.23)	7.44 (6.36 to 8.68)	12.01 (10.38 to 13.87)	0.35 (0.25 to 0.49)	0.39 (0.30 to 0.50)	0.73 (0.57 to 0.95)	0.23 (0.17 to 0.32)	0.73 (0.56 to 0.94)	0.96 (0.76 to 1.21)

Continued

Table 2 Continued

	Prevalence % of mild SCH (95% CI)			Prevalence % of severe SCH (95% CI)			Prevalence % of OH (95% CI)		
	Men	Women	Total	Men	Women	Total	Men	Women	Total
Rural	4.83 (4.11 to 5.68)	7.52 (6.65 to 8.48)	12.35 (10.81 to 14.06)	0.22 (0.15 to 0.32)	0.55 (0.46 to 0.67)	0.77 (0.62 to 0.96)	0.30 (0.22 to 0.41)	0.78 (0.65 to 0.93)	1.07 (0.88 to 1.30)
P for difference	0.48	0.75	0.61	0.16	0.03	0.58	0.10	0.45	0.21
Inland/coastal									
Inland	5.3 (4.82 to 5.84)	8.5 (7.83 to 9.23)	13.81 (12.69 to 15.00)	0.36 (0.25 to 0.52)	0.53 (0.46 to 0.61)	0.90 (0.74 to 1.09)	0.29 (0.22 to 0.38)	0.89 (0.77 to 1.02)	1.17 (1.00 to 1.37)
Coastal	3.81 (3.31 to 4.39)	5.98 (5.24 to 6.82)	9.79 (8.61 to 11.12)	0.17 (0.13 to 0.23)	0.37 (0.27 to 0.50)	0.54 (0.44 to 0.66)	0.24 (0.15 to 0.38)	0.56 (0.42 to 0.75)	0.80 (0.59 to 1.09)
P for difference	< 0.001	<0.001	< 0.001	0.008	0.02	0.002	0.43	0.005	0.02
Cigarette smoking									
Never smoked	5.48 (5.06 to 5.92)	7.52 (6.97 to 8 to 10)	12.99 (12.07 to 13.97)	0.32 (0.21 to 0.50)	0.47 (0.41 to 0.54)	0.79 (0.64 to 0.98)	0.27 (0.22 to 0.32)	0.76 (0.66 to 0.87)	1.03 (0.91 to 1.16)
Smoker	3.96 (3.56 to 4.41)	6.30 (4.83 to 8.18)	10.26 (8.77 to 11.97)	0.24 (0.18 to 0.31)	0.38 (0.18 to 0.83)	0.62 (0.39 to 0.99)	0.27 (0.18 to 0.38)	0.64 (0.40 to 1.01)	0.90 (0.63 to 1.30)
P for difference	<0.001	0.20	<0.001	0.32	0.50	0.001	0.86	0.71	<0.001
Consumption of iodised salt									
Yes	4.71 (4.37 to 5.08)	7.58 (7.07 to 8.13)	12.30 (11.49 to 13.15)	0.29 (0.22 to 0.38)	0.47 (0.41 to 0.53)	0.75 (0.65 to 0.88)	0.27 (0.21 to 0.35)	0.77 (0.67 to 0.88)	1.04 (0.90 to 1.20)
No	4.03 (2.75 to 5.87)	5.58 (4.01 to 7.71)	9.61 (6.85 to 13.33)	0.20 (0.09 to 0.42)	0.52 (0.29 to 0.96)	0.72 (0.48 to 1.08)	0.21 (0.10 to 0.45)	0.53 (0.29 to 0.96)	0.74 (0.43 to 1.26)
P for difference	0.57	0.03	0.16	0.21	0.72	0.95	0.73	0.27	0.42
AIT status									
AIT+	8.89 (8.02 to 9.86)	10.64 (9.82 to 11.53)	19.54 (18.08 to 21.08)	1.27 (0.98 to 1.65)	1.39 (1.14 to 1.69)	2.66 (2.23 to 3.18)	1.48 (1.03 to 2.11)	2.57 (2.12 to 3.10)	4.05 (3.31 to 4.94)
AIT–	4.34 (3.97 to 4.75)	6.68 (6.10 to 7.32)	11.02 (10.11 to 12.01)	0.19 (0.13 to 0.28)	0.23 (0.18 to 0.28)	0.42 (0.33 to 0.53)	0.15 (0.11 to 0.20)	0.28 (0.24 to 0.34)	0.43 (0.36 to 0.52)
P for difference	0.14	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	< 0.001

AIT, autoimmune thyroiditis; BMI, body mass index; OH, overt hypothyroidism; SCH, subclinical hypothyroidism.

appropriate statistical methods. Categorical variables were expressed as counts and percentages and analysed via a χ^2 test. Continuous variables were analysed using analysis of variance (ANOVA). To assess the relationship between hypothyroidism and other factors, we used multivariate logistic regression analysis. The dependent variables included age, gender, smoking status, coastal or inland residence, TPOAb, TgAb, UI and body mass index (BMI). A p value <0.05 was considered statistically significant. All statistical tests were conducted using SPSS (V.23.0; SPSS, Chicago, Illinois) and SUDAAN (V.10.0; Research Triangle Institute).

RESULTS

Demographics of the survey population

A total of 80 937 people were invited to participate in the survey in China (online supplemental figure 1). After excluding individuals with incomplete information, the final analysis included 78 470 participants (38 182 male and 40 288 female). Table 1 lists the demographic and sociological characteristics of the study population based on hypothyroidism severity. The majority of the subjects enrolled were of Han ethnicity. The proportion of hypothyroidism patients with a college or higher education level was not as high as euthyroid subjects. The percentage consumption of iodised salt in different groups was 94.7%–95.8%. The proportion of coastal population among hypothyroidism patients was 15.7%–23.0%.

Prevalence of hypothyroidism

The prevalence of hypothyroidism was 13.95% of the total population; of which OH, severe SCH and mild SCH accounted for 7.81%, 6.19% and 86.00%, respectively. After adjusting for age and gender of the population, the prevalence of OH was 1.02% (95% CI 0.88% to 1.18%), which was significantly higher in women than in men (1.53% vs 0.53%, p<0.001). The prevalence of mild and severe SCH was 12.18% (95% CI 11.31% to 13.10%) and 0.75% (95% CI 0.65% to 0.87%), respectively. Prevalence of both types of SCH was significantly higher in women than in men (mild SCH 15.12% vs 9.30%, p<0.001; severe SCH 0.94% vs 0.56%, p<0.001) (table 2).

Of the 941 subjects with OH, only 71 had received a diagnosis before. The rate of known hypothyroidism was 7.55%. Of the 11 109 subjects with SCH, 280 had received a diagnosis. The rate of known SCH was 2.52%.

Gender, age and hypothyroidism

The prevalence of OH increased with age in both men and women, the prevalence of OH was lowest in the 18–29 age group, and highest in the ≥60 age group (0.45% vs 1.71%, p<0.001; table 2). The prevalence of both mild and severe SCH was lowest in the 30–39 age group, and highest in the ≥60 age group (mild SCH 9.6% vs 16.3%, p<0.001; severe SCH 0.5% vs 1.1%, p<0.001; figure 1). In multivariable-adjusted analyses, female and older age were risk factors for hypothyroidism, severe SCH and mild SCH. The prevalence of mild SCH, severe SCH and OH increases by 1.16%, 1.40% and 1.29% for every 10 years older (table 3).

Thyroid autoantibody and hypothyroidism

The rate of positive TPOAb and/or TgAb in subjects with elevated serum TSH was 39.0%. As the severity of hypothyroidism increased, so did the rate of positive thyroid antibody, including isolated TPOAb, isolated TgAb, coexisting TPOAb+ and TgAb+ as well as AIT (table 4). AIT-related OH, severe SCH and mild SCH accounted for 59.2%, 46.5% and 24.1% respectively. The prevalence of hypothyroidism, severe SCH and mild SCH caused by AIT was higher than others (table 2). Regardless of whether the thyroid autoantibodies were positive, the prevalence of severe SCH and OH was significantly increased with age (figure 2A). However, the prevalence of mild SCH only increased with age in thyroid autoantibody-negative populations (figure 2B).

Multivariate regression showed that compared with TPOAb <20 IU/mL, the risk of hypothyroidism was 17.0-fold greater in TPOAb >500 IU/mL, 14.9-fold greater in subjects with severe SCH and 3.7-fold greater in subjects with mild SCH. Compared with TgAb <20 IU/mL, the risk of hypothyroidism was 6.3 times greater in TgAb >500 IU/mL, 4.0 times greater in severe SCH and 2.0 times greater in mild SCH (figure 3).

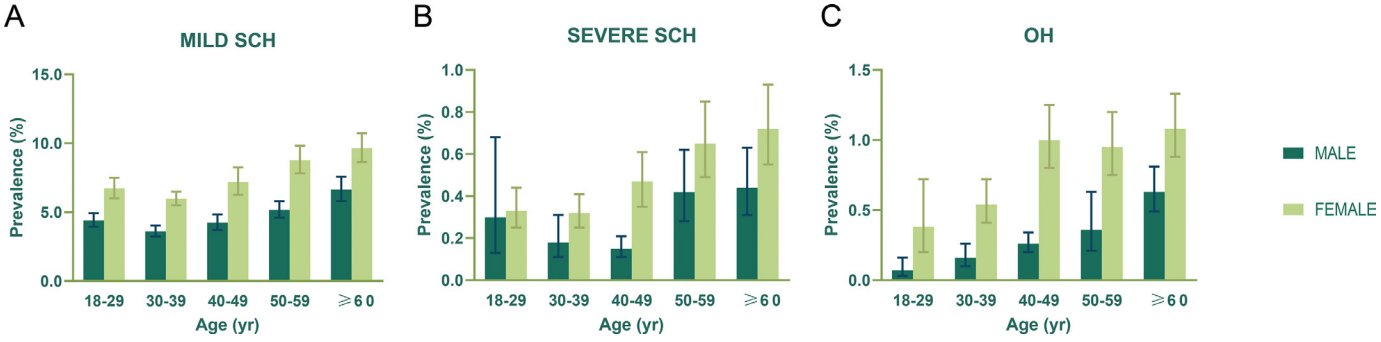

Figure 1 Age-standardised and gender-standardised prevalence rates of mild SCH (A), severe SCH (B), OH (C) and SCH+OH (D). Data are prevalence (%) and 95% CI. OH, overt hypothyroidism; SCH, subclinical hypothyroidism.

Table 3 Multiple-adjusted ORs for SCH or OH associated with risk factors in the general Chinese adult population

	Mild SCH		Severe SCH		OH		Severe SCH+OH	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Female	1.37 (1.30 to 1.44)	<0.001	1.13 (0.94 to 1.35)	0.20	2.14 (1.76,2.60)	<0.001	1.56 (1.36 to 1.78)	<0.001
Age (every 10-year difference)	1.16 (1.15 to 1.18)	<0.001	1.40 (1.33 to 1.48)	<0.001	1.29 (1.23 to 1.36)	<0.001	1.36 (1.31 to 1.41)	<0.001
Inland resident	1.35 (1.28 to 1.43)	<0.001	1.24 (1.00 to 1.54)	0.047	1.32 (1.10 to 1.59)	0.003	1.29 (1.12 to 1.49)	<0.001
Smoker	0.66 (0.62 to 0.71)	<0.001	0.61 (0.48 to 0.76)	<0.001	0.81 (0.64 to 1.02)	0.069	0.68 (0.57 to 0.80)	<0.001
Family history of thyroid disease	1.11 (1.01 to 1.23)	0.032	1.29 (0.93 to 1.78)	0.127	1.90 (1.48 to 2.44)	<0.001	1.66 (1.35 to 2.03)	<0.001
Less than college education	0.95 (0.90 to 1.00)	0.045	0.96 (0.79 to 1.17)	0.69	1.36 (1.11 to 1.65)	0.003	1.16 (1.00 to 1.34)	0.046
BMI, kg/m^2	1.01 (1.01 to 1.02)	<0.001	1.02 (0.99 to 1.04)	0.16	1.06 (1.04 to 1.08)	<0.001	1.04 (1.03 to 1.06)	<0.001
UIC, µg/L								
<100	0.90 (0.84 to 0.96)	0.012	0.91 (0.73 to 1.14)	0.423	1.43 (1.19 to 1.72)	0.003	1.19 (1.03 to 1.38)	0.019
100–199	1.00 (Ref)	–	1.00 (Ref)	–	1.00 (Ref)	–	1.00 (Ref)	–
200–299	1.08 (1.02 to 1.14)	0.008	1.20 (0.98 to 1.47)	0.074	1.26 (1.04 to 1.53)	0.016	1.23 (1.06 to 1.42)	0.005
300–499	1.25 (1.17 to 1.34)	<0.001	1.42 (1.12 to 1.81)	0.04	1.13 (0.88 to 1.45)	0.334	1.28 (1.07 to 1.52)	0.008
≥500	1.59 (1.46 to 1.73)	<0.001	2.03 (1.53 to 2.68)	<0.001	1.59 (1.19 to 2.12)	0.002	1.82 (1.48 to 2.24)	<0.001

BMI, body mass index; OH, overt hypothyroidism; SCH, subclinical hypothyroidism; UIC, urinary iodine concentration.

Urine iodine concentration and hypothyroidism

Increasing urinary iodine concentration (UIC) was associated with increased prevalence of mild SCH in both men and women (figures 2C and 4A). Further analysis found that in the subjects who were thyroid autoantibody negative, the prevalence of mild SCH increased with increasing urinary iodine levels (p for trend <0.001). However, this trend was not found in the case of thyroid autoantibody-positive mild SCH (figure 2). It is suggested that the increase in UIC was the main reason for mild SCH without AIT.

There was a U-shaped association between UIC and OR of severe SCH and OH subjects (figure 4B). However, only men and thyroid autoantibody-negative individuals showed a statistically significant difference between the stratified UIC category (figure 2D,F). Both more than iodine intake and excessive iodine intake were positively correlated with mild SCH, severe SCH and OH. Iodine deficiency was a risk factor for severe SCH and OH, but it was a protective factor for mild SCH (table 3).

Smoking, BMI and hypothyroidism

In multivariable-adjusted analyses, smoking was a protective factor for mild and severe SCH; however, the protective effect of OH disappeared (table 3).

The prevalence of mild SCH in women was significantly higher in BMI ≥25 kg/m^2 than in BMI 18.5–24.9 kg/m^2 and in BMI <18.5 kg/m^2 group (7.89% vs 7.44% vs 7.30%, p for trend <0.05) (table 2). Prevalence of both men and women of OH was significantly higher in BMI ≥25 kg/m^2 than the other groups (men 0.29% vs 0.23% vs 0.23%, p for trend <0.001; women 0.92% vs 0.68% vs 0.35%, p<0.05) (table 2). In multivariable-adjusted analyses, BMI was a risk factor for mild SCH and OH subjects (table 3).

DISCUSSION

Our study showed that the prevalence of hypothyroidism in Chinese adults was 13.95%. Of this, the prevalence of OH, mild and severe SCH were 1.02%, 12.18% and 0.75%, respectively. SCH accounted for 91.1% of all elevated TSH individuals. The estimated total number of adults with SCH in China is 136 million, of which 52 million are men and 83 million are women. The total number of subjects with hypothyroidism is estimated at more than 10.7 million, of which 2.8 million are men and 7.9 million are women.

There have been many studies reporting the prevalence of hypothyroidism worldwide,[4 11 12] with a range of

Table 4 Prevalence of TPOAb and TgAb according to thyroid dysfunction subtypes

	Euthyroid N (%)	Mild SCH N (%)	Severe SCH N (%)	OH N (%)	P
TPOAb positive	4032 (6.7)	1897 (18.3)	306 (41.0)	487 (51.8)	<0.001
TgAb positive	4095 (6.8)	1799 (17.4)	254 (34.0)	446 (47.4)	<0.001
TPOAb+/TgAb+	1926 (3.2)	1202 (11.6)	213 (28.3)	376 (40.0)	<0.001
AIT	6201 (10.3)	2494 (24.1)	347 (46.5)	557 (59.2)	<0.001

AIT, autoimmune thyroiditis; OH, overt hypothyroidism; SCH, subclinical hypothyroidism.

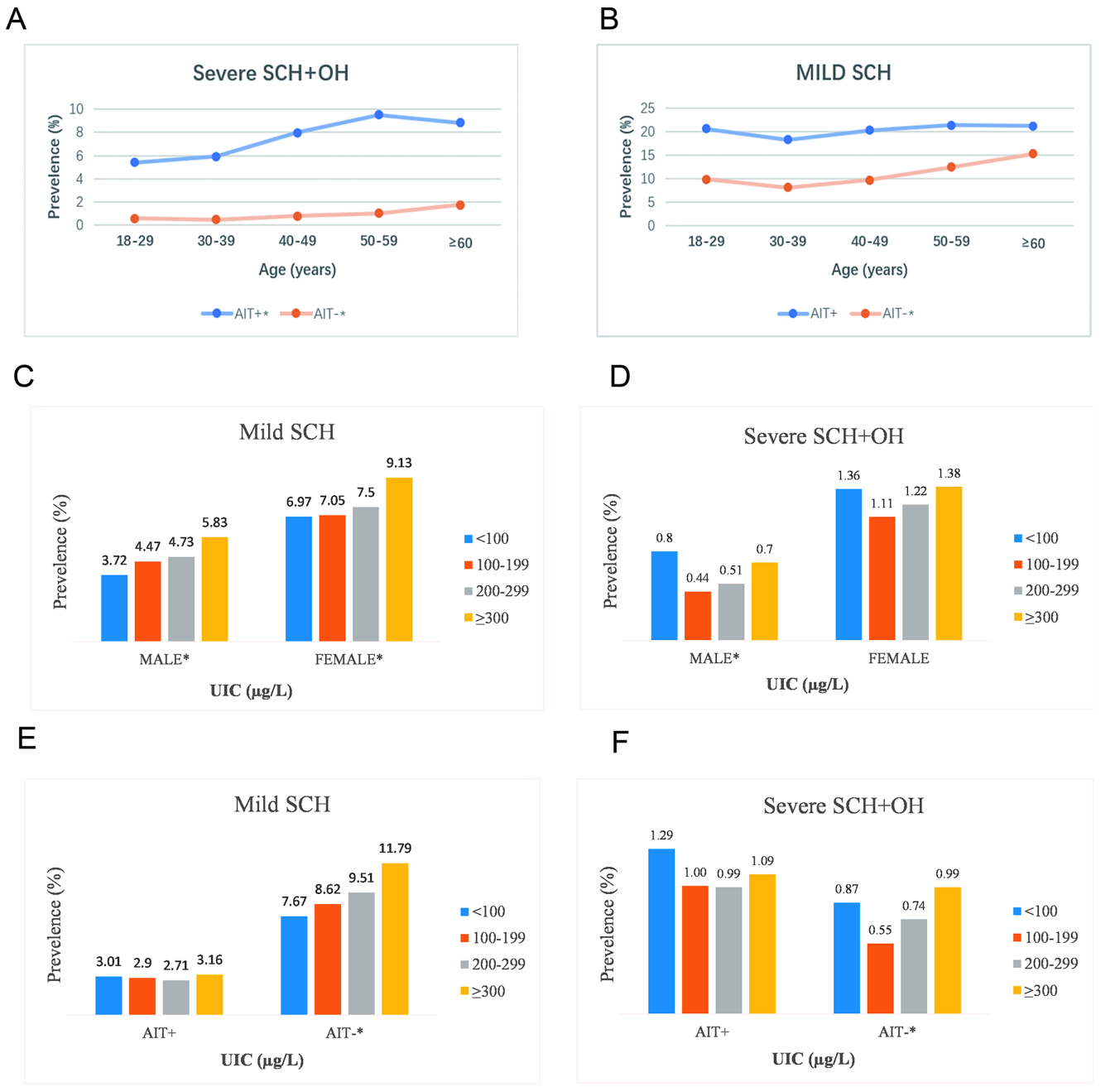

Figure 2 (A) Prevalence rates of severe thyroid dysfunction with different thyroid antibody status stratified by age. *P<0.05 for trend. (B) Prevalence rates of mild SCH with different thyroid antibody status stratified by age. *P<0.05 for trend. (C) Age-standardised prevalence rates of mild SCH among male and female participants stratified by UIC. *P<0.05 for trend. (D) Age-standardised prevalence rates of severe thyroid dysfunction among male and female participants stratified by UIC. *P<0.05 for trend. (E) Age-standardised prevalence rates of mild SCH with different thyroid antibody status stratified by UIC. *P<0.05 for trend. (F) Age-standardised prevalence rates of severe thyroid dysfunction with different thyroid antibody status stratified by UIC. *P<0.05 for trend. SCH, subclinical hypothyroidism; UIC, urinary iodine concentration.

0.3%–3.7% in the USA and 0.2%–5.3% in Europe.[4–8] The prevalence of SCH varied between 3% and 15%.[6 9] Mainland China has implemented a USI policy since 1996, in 1999 and 2004, our group surveyed three rural communities respectively and found that the prevalence of hypothyroidism was 0.27%–1.96%, and the prevalence of SCH was 0.91%–6.05%.[12] From 2011 to 2012, among the 15 008 people surveyed in 10 cities in China, the prevalence of OH was 1.11%, and the prevalence of SCH was 16.7%.[18] Compared with the results above, the prevalence of OH in China has remained relatively stable, however, the prevalence of SCH has increased since 1999 and kept stable over the past 5 years.

As recommended by various guidelines, SCH is further divided into mild and severe SCH. A TSH of 10 mU/L is commonly used to be a cut-off value.[19] Our study found that 93% of subjects with SCH had it to a mild degree, with a TSH level below 10 mU/L. This

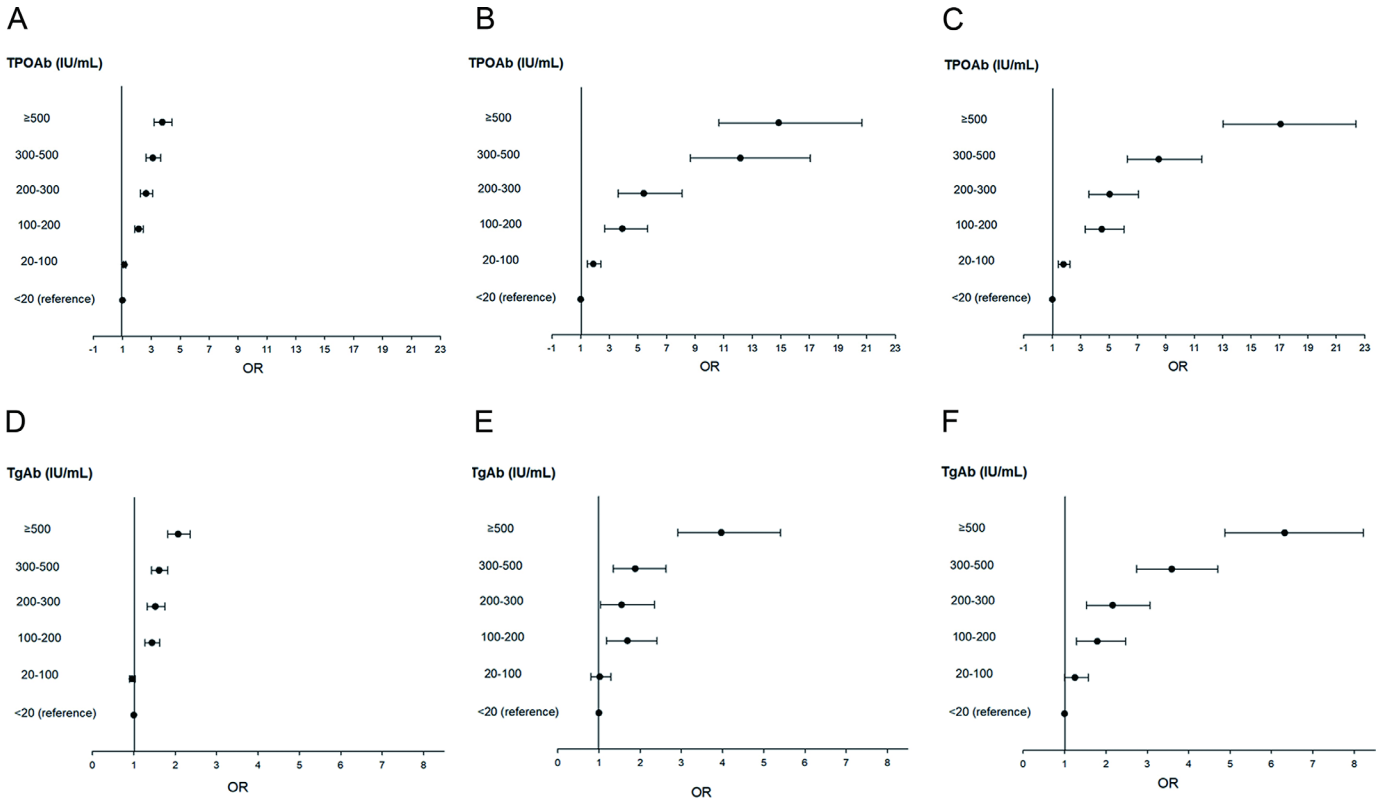

Figure 3 (A) Adjusted associations of TPOAb with mild SCH. (B) Adjusted associations of TPOAb with severe SCH. (C) Adjusted associations of TPOAb with OH. Adjusted for age, gender, location, smoking, family history of thyroid disease, altitude, education level, UIC level and TgAb. (D) Adjusted associations of TgAb with mild SCH. (E) Adjusted associations of TgAb with severe SCH. (F) Adjusted associations of TgAb with OH. Adjusted for age, gender, location, smoking, family history of thyroid disease, altitude, education level, UIC level and TPOAb. OH, overt hypothyroidism; SCH, subclinical hypothyroidism; TgAb, thyroglobulin antibody; TPOAb, thyroid-peroxidase antibody; UIC, urinary iodine concentration.

is consistent with previous studies, which found that 75.0–90.2% of subjects with SCH had TSH levels <10 mU/L.[6 20] Severe SCH accounted for only 7% of hypothyroidism, but its risk factors and immune abnormalities were more inclined to OH. The prevalence of severe SCH and OH caused by AIT was 46.5% and 59.2%, respectively. AIT was the main cause of severe SCH and OH.

Many studies suggest that TPOAb is the main marker of autoimmune abnormalities in hypothyroidism,[21 22] ATA guidelines recommend that if TPOAb is negative, further testing for TgAb. However, the relationship between hypothyroidism and TgAb is limited and unclear.[8] Our study found that compared with TPOAb <20 IU/mL, subjects with TPOAb >500 IU/mL had a much greater risk of OH and severe SCH. Besides,

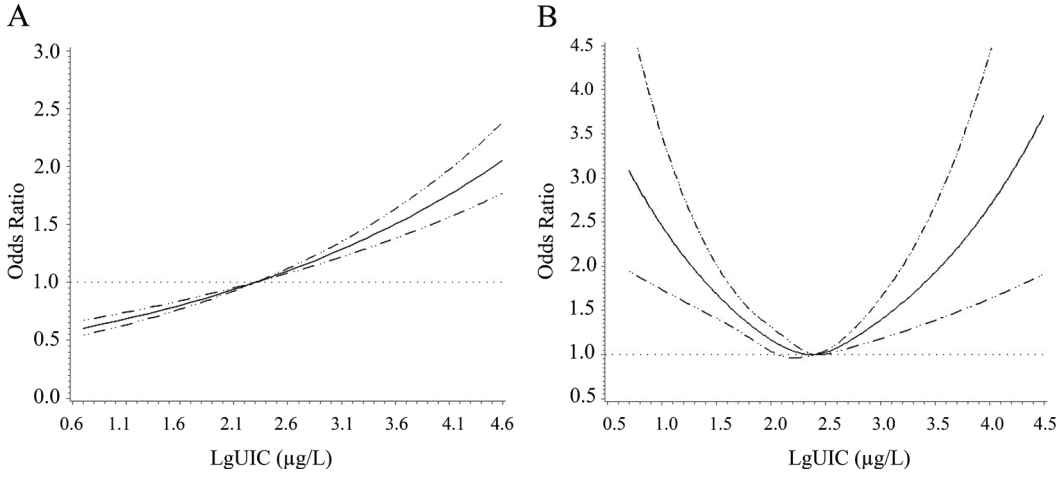

Figure 4 (A) OR for mild SCH based on different levels of lgUIC. (B) OR for severe SCH and OH based on different levels of lgUIC. OH, overt hypothyroidism; SCH, subclinical hypothyroidism; UIC, urinary iodine concentration.

compared with TgAb <20 IU/mL, subjects with a TgAb >500 IU/mL also had a higher risk of OH and severe SCH. Although OH and SCH were associated with both TPOAb and TgAb, TPOAb was a stronger predictor than TgAb for the risk factors for OH and severe SCH.

We found that the TPOAb- and TgAb-positive rate in mild SCH was 24.1%, suggesting that the mild SCH in 76% of subjects was not related to autoimmunity. The present study indicates that there are different mechanisms between OH, severe SCH and mild SCH.

There are many reports of the effects of iodine intake on hypothyroidism.[23 24] The relationship between the level of iodine intake and the occurrence of OH is U-shaped, meaning that the risk of hypothyroidism increases with both low (UIC <50 µg/L) and high (UIC >200 µg/L) iodine intake.[25] Szabolcs *et al*[26] found that the prevalence of SCH was 4.2%, 10.4% and 23.9% for UIC levels of 72 mg/L, 100 mg/L and 513 mg/L, respectively. They also found that SCH occurred more frequently in areas with abundant iodine intake. A meta-analysis[27] pointed out that the prevalence of SCH in excessive iodine intake areas (UIC >300 µg/L) was higher than in areas with deficient (UIC <100 µg/L) and adequate (UIC 100–299 µg/L) iodine areas.

Our results also found that Iodine intake has different effects on OH, severe SCH and mild SCH. The prevalence of severe SCH and OH was also associated with iodine nutrition in a U-shaped relationship in subjects who were thyroid autoimmune antibody negative, However, this trend was not seen in autoimmune-positive subjects. The prevalence of mild SCH statistically increased with increasing urine iodine concentration, which mainly affected autoimmune antibody-negative subjects with mild SCH, but the difference was not statistically significant in the antibody-positive group. This suggests that the effect of iodine nutrition on hypothyroidism was mainly manifested in mild SCH with a non-autoimmune origin. Multivariate analysis also suggests that iodine intake is positively correlated with mild SCH but has a U-shaped correlation with OH and severe SCH.

Though the smoking is risk factor for many diseases, this study found that smoking was a protective factor in the onset of SCH. The effects of smoking on hypothyroidism were inconsistent in different studies which may be affected by iodine nutrition. A study in an iodine-deficient area in India and an iodine-sufficient area in Korea also found that smoking reduced serum TSH levels.[28 29] Research by Park *et al* also showed that smoking reduced TSH levels at different iodine levels and smoking status was not associated with iodine intake.[30] Some studies have reported no association between serum TSH levels and smoking.[31 32] The relationship between hypothyroidism and smoking needs the in-depth analysis. Smoking is harmful to health, the results of this study should not be used to encourage smoking.

We also found that BMI was a risk factor for mild SCH and OH patients. Thyroid function tests were often requested when investigating obese or overweight patients, it is unclear whether raised thyrotropin is a cause or consequence of obesity.[33] Two studies showed normalisation of thyrotropin after weight loss,[34 35] it suggested that a portion of the elevated thyrotropin was an adaptive response of the hypothalamic-pituitary axis to weight gain in an attempt to enhance resting energy expenditure.[36]

A 2013 study in India showed that the prevalence of hypothyroidism in inland areas was higher than in coastal cities.[37] Another study in China found the median UIC for the participants from the inland (188.5 µg/L) was significantly higher than those from the coast (128.5 µg/L; $p<0.001$). The percentage of hypothyroidism was significantly higher for the participants from the inland (17.5%) than those from the coast (7.2%; $p<0.001$).[38] A survey in Shanghai, China, yielded similar results.[39] We also found this phenomenon for both OH and SCH. The iodine nutrient concentration in coastal areas was lower than in inland areas, which was possibly related to the lower consumption of iodised salt in coastal areas. There were two main reasons. First, coastal residences considered they could supplement iodine through seafood, they were more likely to consume non-iodised salt or intermittently consumed. Second, the coastal population was accustomed to lighter taste than those from the inland.[40]

After 20 years of adjusting the concentration of USI, the prevalence of OH has decreased and the prevalence of SCH has increased, while the prevalence of hyperthyroidism, AIT and goitre have all decreased significantly,[16] we need to continue monitoring. Our survey showed that the USI had been successful, not only in preventing iodine deficiency disorders but also in reducing the incidence of most thyroid diseases.

There are several limitations to this article. First, the study is a cross-sectional investigation, this study was unable to reveal the mechanisms involved in the observed phenomena. Second, epidemiological investigations on such a large national scale are methodologically challenged by geographic, environmental, genetic and other factors. Finally, this study was an epidemiological investigation and cannot be repeated TSH testing like the clinical diagnosis of SCH.

CONCLUSION

The prevalence of hypothyroidism is high in the adult Chinese population which is mainly mild SCH. The clinical manifestations of severe SCH tend to be OH, which is related to thyroid autoimmune abnormalities. Iodine deficiency and excess iodine are positively correlated with OH and severe SCH. Mild SCH is positively correlated with iodine intake, mainly manifested in non-thyroid autoimmune SCH.

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Contributors ZS, WT, DT, XS and XT conceived and designed the study. ZS and WT supervised the study.ZS and WT drafted the manuscript. JL and YL performed the statistical analysis. All authors contributed to the acquisition, analysis, or interpretation of data. All authors revised the report and approved the final version before submission.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval This study involves human participants and was approved by Medical Ethics Committee of China Medical University (IRB-2013-115). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The datasets generated and analysed during the current study are not publicly available because we promised that the data will not be provided to the third parties when reviewed by the ethics committee. Data are available upon reasonable request.

ORCID iDs
Yongze Li http://orcid.org/0000-0001-8782-3314
Zhongyan Shan http://orcid.org/0000-0002-2849-2380

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