Association of longitudinal changes in serum lipids with the natural history of subclinical hypothyroidism: A retrospective cohort study using data from the REACTION study

Fang Zhong,[a,b] *Qingbo Guan,*[a,b,c] *Haiqing Zhang,*[a,b,c] *Xu Zhang,*[a,b,c] *Meng Zhao,*[a,b,c] *Zhongshang Yuan,*[d] *Xiude Fan,*[a,b,c] *Junming Han,*[a,b,c] *Qihang Li,*[a,b] *Zhixiang Wang,*[a,b] *Shanshan Shao,*[a,b,c] *and Jiajun Zhao*[a,b,c]*

[a]Department of Endocrinology, Shandong Provincial Hospital, Shandong University, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, 250021, China
[b]Shandong Clinical Medical Centre of Endocrinology and Metabolism, Jinan, Shandong, 250021, China
[c]Shandong Institute of Endocrine and Metabolic Disease, Jinan, Shandong, 250021, China
[d]Department of Biostatistics, School of Public Health, Shandong University, Jinan, 250021, China

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Summary

Background Subclinical hypothyroidism (SCH) often leads to alterations in lipid profile, which may negatively impact humans health. Whether lipids in turn affect the natural history of SCH is unknown. We aimed to assess the association between longitudinal changes in serum lipid levels and the natural history of SCH.

Methods This retrospective cohort study using data from the REACTION study included 581 patients with SCH who were enrolled between July 1, 2011, and December 19, 2014, with a median follow-up of three [IQR, 2·86-3·21] years. Patients with missing data or conditions that can affect thyroid function were excluded. Changes in serum lipid levels were calculated from serum lipid measurements 3 years apart and classified in two ways: 1) the first, second, and third tertiles of the difference between baseline and follow-up and 2) the percent change from baseline, namely, serum lipid decrease ≥ 25%, minor change, and serum lipid increase ≥ 25%. The natural history of SCH includes regression to euthyroidism, SCH persistence, or progression to overt hypothyroidism (OH). Odds ratios (ORs) were estimated by multivariable logistic regression. Validation was performed on data from a health management cohort study conducted from January 1, 2012, to December 31, 2016, with a median follow-up of two [IQR, 1·92-2·08] years. After using the same inclusion and exclusion criteria as the REACTION cohort study, 412 patients with SCH were eligible for the validation analysis.

Findings There were 132 (22·7%) men and 449 (77·3%) women in the study, with a median age of 56 [IQR,49-62] years. During follow-up, 270 (46·5%), 266 (45·8%), and 27 (4·6%) patients had regression to euthyroidism, persistent SCH, and progression to OH, respectively. Both grouping manners showed a significant association between changes in lipid levels and the natural history of SCH. A total cholesterol (TC)-level increase was independently associated with a greater risk of progression to OH (OR for ≥ 25% TC increase vs. minor change: 5·40; 95% CI 1·46-21·65), whereas TC-level declines increased the likelihood of regressing to euthyroidism (OR for ≥ 25% TC decrease vs. minor change: 3·45; 95% CI 1·09-12·43). Similarly, the likelihood of regression according to changes in triglyceride (TG) levels exhibited a consistent trend with that according to TC-level changes. A similar pattern of association was observed in the validation cohort.

Interpretation Changes in serum lipid levels in SCH are associated with future progression or regression risk, suggesting that the changes in serum lipid levels may affect the natural history of SCH. Clinicians should pay attention to the long-term control of serum lipids levels in populations with SCH, which may benefit thyroid function.

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Abbreviations: SCH, Subclinical hypothyroidism; TSH, thyroid-stimulating hormone; FT4, free thyroxine; OH, overt hypothyroidism; TG, triglyceride; TC, total cholesterol; eGFR, estimated glomerular filtration rate; Cr, creatinine; FT3, free triiodothyronine; TPOAb, thyroperoxidase antibody; ALT, alanine transaminase; HbA1c, glycatedhaemoglobin; SBP, systolic blood pressure

*Corresponding author at: Department of Endocrinology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, 324, Jing 5 Rd, Jinan, Shandong, 250021, China.
E-mail address: jjzhao@sdu.edu.cn (J. Zhao).

Keywords: Lipid; Cholesterol; Triglyceride; Thyroid; Subclinical hypothyroidism; Hypothyroidism; Cohort study

Research in context

Evidence before this study

We searched PubMed for studies published until May 05, 2022, using search terms lipid, cholesterol, TC, triglyceride, TG, hyperlipidemia or dyslipidemia and hypothyroidism, subclinical hypothyroidism, thyroid function or thyroid with search terms found in abstract, title or MESH headings. We also searched references listed in the identified papers. Previous studies have indicated that dyslipidaemia is traditionally thought to be the result of hypothyroidism. However, little is known regarding the reverse relationship between them. Interestingly, an adverse effect of lipids on the thyroid has also been suggested in recent studies. SCH is the early stage of hypothyroidism but also may be transitory. This means that it may progress or regress. Identifying the factors influencing this course is beneficial to prognosis. Dyslipidemia is the most common metabolic disorder in patients with SCH, whether lipids can in turn affect the natural history of SCH is unknown.

Added value of this study

To the best of our knowledge, this cohort study is the first to show that changes in serum lipid levels were related to the natural history of SCH. A dynamic increase in total cholesterol (TC) levels increases the risk of progression to overt hypothyroidism (OH), while a dynamic decrease in TC and triglyceride (TG) levels is associated with a higher likelihood of regression to euthyroidism.

Implications of all the available evidence

Dynamic changes in serum lipid levels are associated with corresponding changes in the risk of future progression or reversion in people with SCH. The available results indicate a dire need for long-term control of TC and TG levels in populations with SCH, which may be benefit to the thyroid function in SCH.

Introduction

Subclinical hypothyroidism (SCH), defined as elevated levels of serum thyroid-stimulating hormone (TSH) in combination with normal levels of serum free thyroxine (FT4), affects up to 10% of the iodine-sufficient population.[1] In recent years, SCH has attracted extensive attention for its long-term adverse effects, particularly with respect to the risk of cardiovascular disease.[2] Other possible adverse consequences include disordered lipid metabolism, cognitive decline, neuromuscular dysfunction, and lower ovarian reserve.[3–5]

SCH is the early stage of hypothyroidism but may also be transitory. This means that it may progress to overt hypothyroidism (OH) or regress to euthyroidism. The risk of SCH progression to OH is approximately 2-6% per year.[6] On the other hand, thyroid function normalises spontaneously in up to 35-67·5% of patients with SCH within 5 years.[7–9] Progression to OH further increases the risk of the aforementioned adverse consequences, so factors that affect the natural history of SCH have become a research focus. It has been reported that initial TSH levels, FT4 levels, thyroid autoantibody levels, thyroid ultrasonography findings, and iodine intake can serve as prognostic factors for the natural history of SCH.[9,10]

Dyslipidaemia is traditionally thought to be the result of hypothyroidism,[11] whereas the reverse relationship between them has been ignored. Interestingly, an adverse effect of lipids on the thyroid has also been suggested in recent studies. Our group previously found that the thyroid was one of the target organs of lipotoxicity, and high circulating triglyceride (TG) was a potential risk factor for SCH.[12] The concept of "cholesterol-induced toxicity" has also been proposed, and excess cholesterol accumulation may induce pituitary-thyroid dysfunction.[13] Electron microscopy showed significant lipid droplet accumulation, cytoplasmic loss, and mitochondrial degeneration in the thyroid follicular cells of high-cholesterol diet-fed mice.[14] Meanwhile, our previous cohort study revealed that statin use significantly improved the remission rate of SCH by reducing total cholesterol (TC).[15] These studies suggested that the thyroid gland may be attacked by lipids.

Given that SCH often leads to lipid metabolism disturbance, we should focus in particular on the impact of lipids in the course of SCH. In addition, the effect of lipids on the human body is a chronic and long-term process, and the effect of the long-term state characterized by changes in serum lipids needs to be evaluated. Delineation of the relationship between changes in serum lipids and the natural history of SCH is crucial for the prognosis and effective management of SCH; however, the relationship between them remains unclear. Therefore, we conducted a population-based cohort study to evaluate the longitudinal association of changes in serum lipid levels with the natural history of SCH.

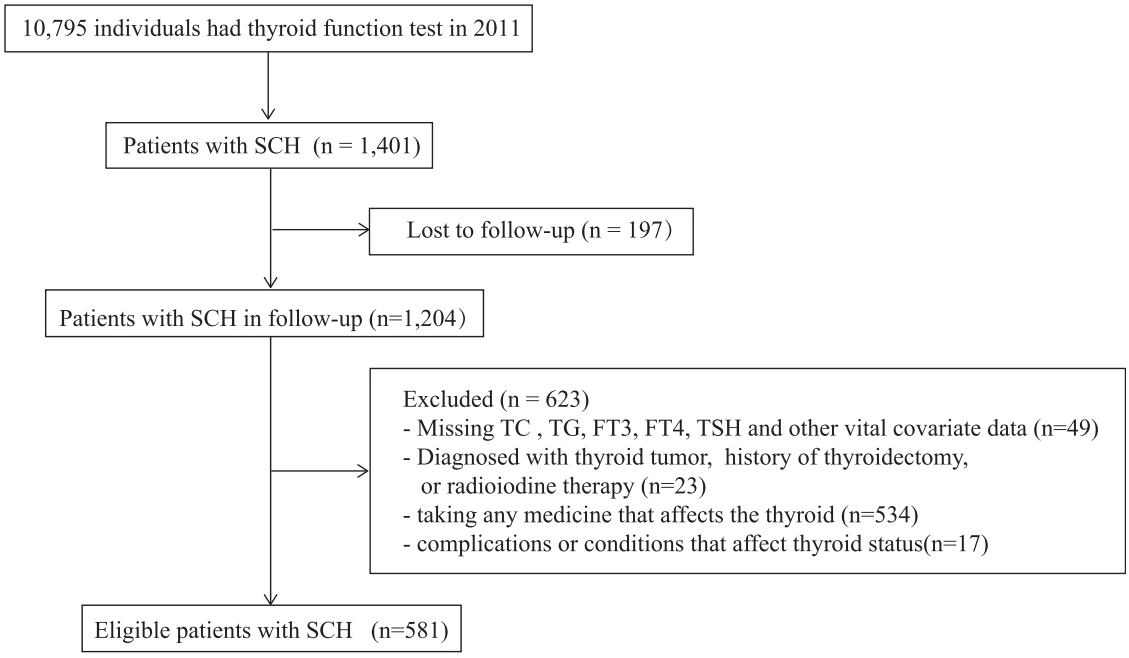

Figure 1. Participant flow diagram. Abbreviations: SCH, subclinical hypothyroidism; TC, total cholesterol; TG, triglyceride; FT3, free triiodothyronine; FT4, free thyroxine.

Methods

Study design and participants

The REACTION study was a population-based, prospective cohort study that enrolled 259,657 Chinese adults (aged ≥40 years) from 25 communities in China between July 1, 2011, and December 19, 2014, with follow-ups planned at 3, 5, and 10 years.[16] Data from one of the 25 communities, in Ningyang County, Shandong Province, were selected for this study. Inhabitants who had lived in their residences for at least 5 years were invited to participate. Overall, 10,795 participants provided an overnight fasting blood sample, underwent thyroid function tests and medical examination, and completed a self-report questionnaire at baseline. Baseline data were collected in 2011 and participants were followed up in 2014. The study was approved by both the central institutional review board and local institutional review boards, and all procedures strictly followed the Declaration of Helsinki. All participants signed written informed consent forms before taking part in the study. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

The following individuals were excluded during the follow-up: (1) patients with missing vital data, such as age, sex, and lipid and thyroid function index (n=49); (2) patients diagnosed with thyroid tumours, and those with a history of thyroidectomy or radioiodine therapy (n=23); (3) patients taking any medicine that affects the thyroid, including thyroid hormones, antithyroid medication, amiodarone, alemtuzumab, lithium, tyrosine kinase inhibitors, interferons, oestrogens, androgens, glucocorticoids, heparin, nonsteroidal anti-inflammatory drugs, antiepileptic drugs, or rifampicin in the past three months (n=534); and (4) patients with complications or conditions that affect thyroid function, including pregnancy, lactation, severe hepatic or renal dysfunction (an estimated glomerular filtration rate (eGFR) lower than 60 mL/min per 1·73 m^2 and creatinine higher than 105 μmol/L) (n=17). Ultimately, 581 individuals were eligible for our study (Figure 1), and all (100%) were included in the analysis.

Data collection

The data collection process was previously described.[12] Trained investigators obtained information on demographic characteristics and other essential information from a standardized questionnaire through in-person interviews. Anthropometric measurements, including height, weight, and waist circumference were performed by trained nurses following a standard protocol. Blood pressure measurements were performed three times with intervals of 3 min on the nondominant arm using an electronic sphygmomanometer (HEM-7117; Omron, Kyoto, Japan) after 5 min of rest. The average of the three measurements was calculated.

All blood samples were collected between 8:00 and 10:00 a.m. after an 8- to 10-h overnight fast. TSH, FT4, free triiodothyronine (FT3), and thyroperoxidase antibody (TPOAb) were measured by chemiluminescence

methods (Cobas E610, Roche, Basel, Switzerland). The serum lipid profile, serum glucose, and hepatic and renal function were measured by the ARCHITECT ci16200 Integrated System (Abbott, Illinois, USA). The intra- and interassay coefficients of variation were below 5% for all parameters. Although we made every effort to minimize the occurrence of data loss, missing data (n=49) were occasionally encountered for several reasons, including uncollected blood samples due to difficulty blood drawing blood or insufficient fasting time.

Study outcome definition

The laboratory reference ranges were as follows: 0·27-4·2 μIU/mL for TSH; 3·1-6·8 pmol/L for FT3; 12-22 pmol/L for FT4; and 0–34 IU/L for TPOAb. OH was defined as a combination of decreased FT4 and elevated TSH, and SCH was defined as a combination of normal FT4 and elevated TSH.[6]

External validation cohort

The validation cohort was recruited from the Health Management Centre of Shandong Provincial Hospital between January 1, 2012, and December 31, 2016. We recruited 7,617 individuals who had three visits and underwent thyroid function tests during this period. Each visit had an interval of more than half a year. Of these individuals, 433 had SCH at the first two visit. After using the same inclusion criteria as outlined above, 412 individuals were eligible for the validation analysis, with the flow diagram displayed in Supplemental Figure 1. This study was also approved by the Ethics Committee of Shandong Provincial Hospital. We obtained informed consent exemptions approved by the ethics committee.

Statistical analyses

Continuous variables are expressed as the means (standard deviations) for normally distributed continuous variables, medians (interquartile ranges) for skewed-distributed continuous variables, or numbers (percentages) for categorical data. Differences among groups were analysed using one-way ANOVA, the Kruskal–Wallis H test, or the chi-square test. Post hoc tests were performed using Bonferroni or Games-Howell comparisons. P for trend was calculated by taking the categorical exposure variables as ordinally continuous variables in logistic regression models. We compared baseline and follow-up measurements using a paired t test and Wilcoxon-paired signed-rank test.

We assessed changes in serum lipids (TC and TG levels) from baseline to 3 years of follow-up. Changes in TC and TG levels were classified into three groups in two different ways: 1) levels were divided into three categories according to tertile distributions of ΔTC and ΔTG (ΔTC or ΔTG level = TC or TG concentration at end of follow-up − TC or TG concentration at baseline); and 2) levels were divided into three categories according to percentage of ΔTC or ΔTG: decrease in TC or TG of ≥ 25%, minor change in TC or TG (decrease in TC or TG < 25% to increase < 25%), and increase in TC or TG ≥ 25%. We chose a 25% change as the cut-off point mainly from the clinical perspective. The change in cholesterol of 25% is a commonly used value in clinical practice. For instance, moderate-intensity statins can reduce blood lipids by 25%,[17] which is recommended as a general treatment regimen for dyslipidaemia according to the Chinese Guidelines on Prevention and Treatment of Dyslipidaemia in adults. We also assessed ΔTC or ΔTG continuously. ΔTC and ΔTG in the validation cohort were also grouped in this way, but we assessed changes in TC and TG levels, calculated using measurements from the first two visits.

We used logistic regression models to assess the association between ΔTC, ΔTG and the natural history of SCH. Before the initiation of analyses, we reviewed the literature and identified all factors that affect thyroid function as potential confounding factors in the multivariate logistic regression models, including age, sex, BMI, TSH, FT3, FT4, TPOAb, creatinine (Cr), smoking status, and alcohol consumption. In addition, we also adjusted TC, and TG levels at baseline to exclude the influence of baseline serum lipids on the natural history of SCH. Considering that different levels of TC and TG at baseline may interfere with ΔTC and ΔTG, we further explored the above relationship according to subsets of participants grouped by TC (TC normal: TC <5·2 mmol/L, TC high: TC ≥ 5·2 mmol/L) and TG (TG normal: TG < 1·7, TG high: TG ≥ 1·7 mmol/L) at baseline.[18] We evaluated the association of changes in TC and TG levels calculated using measurements from the first two visits with the subsequent natural history of SCH at the third visit.

We performed two sensitivity analyses. First, we repeated the analyses excluding individuals taking lipid-lowering medications (n=10). Second, we further adjusted for alanine transaminase (ALT), glycated haemoglobin (HbA1c), and systolic blood pressure (SBP) in the fully adjusted model. A two-tailed P value <0·05 was considered statistically significant. We used R version 4·0·2 to conduct all statistical analyses.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had access to dataset and had final responsibility for the decision to submit for publication.

Results

At baseline, of the 10,795 individuals for whom thyroid function tests were performed, 1401 individuals (13.0%) had SCH. A total of 197 individuals were lost during

	Overall (581)	Euthyroidism (n=270)	SCH (n=266)	OH (n=27)	*P* value
Age (years), mean ± SD	56 ± 9	55 ± 8	57 ± 9 [a]	56 ± 9	0.0030
Sex, n (%)					0.65
Men	132 (22.7)	67 (24.8)	57 (21.4)	6 (22.2)	
Women	449 (77.3)	203 (75.2)	209 (78.6)	21 (77.8)	
BMI (kg/m^2), mean ± SD	25.31 ± 3.77	25.38 ± 3.62	25.15 ± 3.81	26.41 ± 4.65	0.24
SBP (mmHg), mean ± SD	140 ± 21	139 ± 20	141 ± 21	136 ± 20	0.33
FPG (mmol/L), median (IQR)	5.8 (5.4 − 6.4)	5.8 (5.3 − 6.4)	5.7 (5.4 − 6.4)	6.0 (5.6 − 7.0)	0.25
HbA1c (%), median (IQR)	5.9 (5.6 − 6.3)	5.9 (5.6 − 6.3)	5.9 (5.7 − 6.2)	5.9 (5.6 − 6.3)	0.96
TC (mmol/L), mean ± SD	5.19 ± 1.11	5.22 ± 1.13	5.17 ± 1.12	5.24 ± 0.96	0.86
TG (mmol/L), median (IQR)	1.19 (0.88 -1.70)	1.23 (0.90 - 1.78)	1.13 (0.86 -1.63)	1.23 (0.94 - 2.06)	0.32
HDL (mmol/L), mean ± SD	1.46 ± 0.35	1.47 ± 0.35	1.46 ± 0.36	1.44 ± 0.39	0.89
LDL (mmol/L), mean ± SD	3.05 ± 0.86	3.06 ± 0.85	3.04 ± 0.87	3.05 ± 0.77	0.99
AST (IU/L), median (IQR)	21 (18 − 25)	22 (18 − 25)	21 (17 − 25)	21 (19 − 25)	0.36
ALT (IU/L), median (IQR)	16 (12 − 21)	16 (12 − 21)	15 (12 − 19)	19 (13 − 25)	0.10
Cr (μmol/L), mean ± SD	63.50 ± 10.23	63.34 ± 10.63	63.49 ± 10.14	64.56 ± 7.74	0.84
Current smoking patterns, n (%)					0.12
No	514 (88.5)	236 (87.4)	240 (90.2)	21 (77.8)	
Occasionally	43 (7.4)	25 (9.3)	13 (4.9)	4 (14.8)	
Almost everyday	24 (4.1)	9 (3.3)	13 (4.9)	2 (7.4)	
Current drinking patterns, n (%)					0.27
No	472 (81.2)	221 (81.9)	213 (80.1)	21 (77.8)	
Occasionally	78 (13.4)	31 (11.5)	40 (15.0)	6 (22.2)	
Almost everyweek	31 (5.3)	18 (6.7)	13 (4.9)	0 (0.0)	
FT3 (pmol/L), median (IQR)	4.81 (4.35 − 5.25)	4.88 (4.46 − 5.30)	4.68 (4.26 − 5.18) [a]	4.80 (4.56 − 5.04)	0.017
FT4 (pmol/L), median (IQR)	15.27 (14.01 − 16.72)	15.76 (14.47 − 17.05)	15.00 (13.97 − 16.50) [a]	13.52 (12.56 − 14.64) [a b]	<0.0001
TSH (mIU/L), median (IQR)	5.29 (4.65 − 6.52)	4.92 (4.50 − 5.66)	5.66 (4.90 − 7.29) [a]	6.27 (5.09 − 7.42) [a]	<0.0001
TPOAb positive, n (%)	118 (21.5)	47 (18.3)	53 (21.1)	13 (54.2) [a b]	0.0001

***Table 1*: Baseline characteristics of individuals with euthyroidism, SCH, or OH at the end of follow-up.**
Abbreviations: SCH, subclinical hypothyroidism; OH, overt hypothyroidism; BMI, body mass index; SBP, systolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Cr, creatinine; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyrotropin; TPOAb, thyroperoxidase antibody.
[a] $P < 0.05$ vs euthyroidism.
[b] $P < 0.05$ vs SCH.

follow-up, and 623 individuals who had missing data or conditions that can affect thyroid function were excluded based on the exclusion criteria. Ultimately, 581 patients with SCH were included in the analysis (Figure 1).

There were 132 (22·7%) men and 449 (77·3%) women in the study, with a median age of 56 [IQR,49-62] years (Table 1). Among the 581 patients with SCH at baseline, 270 (46·5%) regressed to euthyroidism, 266 (45·8%) had persistent SCH, and only 27 (4·6%) progressed to OH after a median follow-up of three years. Other outcomes included two cases of subclinical hyperthyroidism, 12 cases of isolated decreased FT4 levels, and four cases of isolated increased FT4 levels.

Baseline characteristics of the study participants with different thyroid functions at the end of follow-up

The baseline characteristics of the study's participants were described by different thyroid functions (euthyroid, SCH, and OH) at the end of follow-up (Table 1). Compared with individuals who revert to euthyroidism, individuals with persistent SCH were significantly older and had higher baseline TSH levels and lower baseline FT3 and FT4 levels (all $p < 0·05$). Individuals who progressed to OH had significantly higher baseline TSH levels than individuals with euthyroidism, and had lower baseline FT4 levels and higher baseline TPOAb positivity than both the euthyroidism and SCH groups (all $p < 0·05$). There were no significant differences in serum lipid levels among the three groups. Other sociodemographic and biochemical characteristics are also presented in Table 1.

Changes in TC and TG levels during follow-up

We first investigated whether ΔTC and ΔTG were different in the euthyroid, SCH, and OH groups at the end of follow-up. At a median follow-up of three years, serum TC levels increased from 5·24 ± 0.96 to 6·01 ±

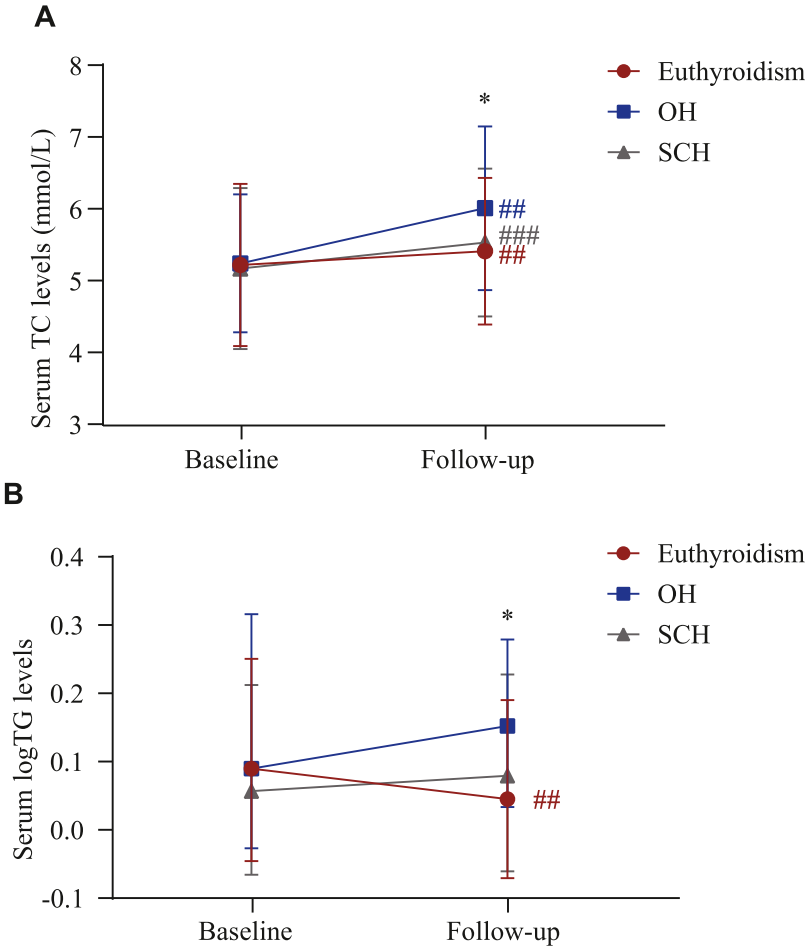

Figure 2. The changes in TC and log-transformed TG levels in three outcomes (euthyroidism, OH, and SCH) of SCH natural history. ##p < 0.01 and ###p < 0.0001, TC or log-transformed TG at follow-up compared with the baseline; *p < 0.05, changes in TC or TG levels in OH group compared with euthyroidism group. (A) Changes of serum TC levels from baseline to the end of follow up in each group. (B) Changes of serum log-transformed TG levels from baseline to the end of follow up in each group. Abbreviations: TC, total cholesterol; TG, triglyceride; SCH, subclinical hypothyroidism; OH, overt hypothyroidism.

1·14 mmol/L (p = 0·0039) in individuals who progressed to OH, from 5·17 ± 1·12 to 5·53 ±1·03 mmol/L (p < 0.0001) in individuals with persistent SCH, and from 5·22 ± 1·13 to 5·41 ±1·02 mmol/L (p = 0·0038) in individuals with euthyroidism (Figure 2A). Although TC levels increased to a significantly different degree in all three groups, the increase was more significant in the OH group than in the euthyroidism group (OH vs. euthyroidism, 0·77 vs. 0·19 mmol/L, p = 0·020) (Figure 2A). For TG, the TG levels tended to be higher in both the OH group (p = 0·42) and SCH group (p = 0·29), while they experienced a significant decrease (Figure 2B) by a median of 0·12 mmol/L (from 1·23 to 1·11 mmol/L) (p = 0·0007) over the 3-year period in the euthyroidism group.

A dynamic increase in TC levels increased the risk of progression to OH, whereas a dynamic decrease in TC levels increased the likelihood of regression to euthyroidism

Overall, we observed a strong positive association between ΔTC and the risk of progression to OH (Table 2). After adjusting for confounding factors such as age, sex, BMI, TSH, FT3, FT4, TPOAb, Cr, smoking, drinking, TC, and TG at baseline, the risk of progression to OH increased progressively as ΔTC increased (P for trend = 0·029), with adjusted ORs for Q2 and Q3 vs. Q1 of 2·09 (0·60-8·03) and 5.11 (1·24-23·83), respectively. When the population was stratified by the percent change based on ΔTC, the risk of progression to OH was significantly higher among individuals with an

	OH				Euthyroidism			
	N total	N event (%)	OR (95%CI)	*P* value	N total	N event (%)	OR (95%CI)	*P* value
Per unit increase in ΔTC			2.79 (1.59-4.98)	0.0004			0.72 (0.57-0.88)	0.0022
Tertile range of ΔTC								
Q1 (< −0.17 mmol/L)	190	5 (2.6%)	1 (ref)		190	101 (53.2%)	1 (ref)	
Q2 (−0.17—0.68 mmol/L)	199	10 (5.0%)	2.09 (0.60-8.03)	0.26	199	89 (44.7%)	0.60 (0.38-0.96)	0.034
Q3 (> 0.68 mmol/L)	192	12 (6.3%)	5.11 (1.24-23.83)	0.029	192	80 (41.7%)	0.47 (0.27-0.79)	0.0053
P for trend				0.029				0.0051
Percentage of ΔTC								
Decrease>25%	18	0 (0%)	-	-	18	13 (72.2%)	3.45 (1.09-12.43)	0.042
Minor (decrease <25% to increase >25%)	447	19 (4.3%)	1 (ref)		447	209 (46.8%)	1 (ref)	
Increase>25%	116	8 (6.9%)	5.40 (1.46-21.65)	0.013	116	48 (41.4%)	0.65 (0.39-1.07)	0.089
P for trend				-				0.016

***Table 2*: Adjusted ORs and 95% CIs for OH and euthyroidism outcome according to longitudinal changes in TC levels.**
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; OH, overt hypothyroidism; ΔTC = TC concentration at end of follow-up − TC concentration at baseline; Q1, Q2, and Q3 represent the first, second, and third tertile of ΔTC; Percentage of ΔTC = ΔTC / TC concentration at baseline *100; -, none of the participants.
ORs (95% CIs) were adjusted for age, sex, BMI, TSH, FT3, FT4, TPOAb, Cr, smoking, drinking, TC, and TG at baseline.

increase in TC of ≥25% (OR 5·40; 95% CI 1·46−21·65, p = 0·013) than among individuals who experienced a minor change in TC (<25% up or down).

Correspondingly, there was a negative association between ΔTC and the likelihood of regression to euthyroidism (Table 2). Compared with Q1, the ORs and 95% CIs of Q2 and Q3 were 0·60 (0·38-0·96) and 0.47 (0·27-0·79), respectively (P for trend = 0·0051). In addition, a decrease in TC of ≥25% was significantly associated with a 3·45-fold (OR 3·45; 95% CI 1·09-12·43, p = 0·042) higher likelihood of reversion compared with a minor change. Adjusted ORs and 95% CIs for OH and euthyroidism outcomes according to other categorical longitudinal changes in TC levels are shown in Supplemental Table 1.

A dynamic decrease in TG levels increased the likelihood of regression to euthyroidism

In terms of changes in TG levels and the natural history of SCH, we did not find statistically significant associations between changes in TG levels and the risk of developing OH. Nevertheless, we observed a strong negative association between ΔTG and the likelihood of regression to euthyroidism (Table 3). Compared with Q1, the adjusted ORs and 95% CIs of Q2 and Q3 were 0·57 (0·35-0·92) and 0·49 (0·30-0·80), respectively

	OH				Euthyroidism			
	N total	N event (%)	OR (95%CI)	*P* value	N total	N event (%)	OR (95%CI)	*P* value
Per unit increase in ΔTG			1.60 (0.82-3.30)	0.20			0.75 (0.58-0.94)	0.019
Tertile range of ΔTG								
Q1 (< −0.23 mmol/L)	197	6 (3.0%)	1 (ref)		197	109 (55.3%)	1 (ref)	
Q2 (−0.23—0.16 mmol/L)	196	9 (4.6%)	1.25 (0.33-4.96)	0.75	196	83 (42.3%)	0.57 (0.35-0.92)	0.023
Q3 (> 0.16 mmol/L)	188	12 (6.4%)	2.16 (0.70-7.53)	0.20	188	78 (41.5%)	0.49 (0.30-0.80)	0.0046
P for trend				0.19				0.0058
Percentage of ΔTG								
Decrease>25%	153	5 (3.3%)	0.85 (0.22-2.92)	0.81	153	88 (57.5%)	1.95 (1.22-3.15)	0.0053
Minor (decrease <25% to increase >25%)	271	13 (4.8%)	1 (ref)		271	116 (42.8%)	1 (ref)	
Increase>25%	157	9 (5.7%)	1.28 (0.42-3.81)	0.66	157	66 (42.0%)	0.96 (0.62-1.50)	0.87
P for trend				0.55				0.013

***Table 3*: Adjusted ORs and 95% CIs for OH and euthyroidism outcome according to longitudinal changes in TG levels.**
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; OH, overt hypothyroidism; ΔTG = TG concentration at end of follow-up − TG concentration at baseline; Q1, Q2, and Q3 represent the first, second, and third tertile of ΔTG. Percentage of ΔTG = ΔTG / TG concentration at baseline*100.
ORs (95% CIs) were adjusted for age, sex, BMI, TSH, FT3, FT4, TPOAb, Cr, smoking, drinking, TC, and TG at baseline.

(P for trend = 0·0058). Compared with individuals with a minor change, the likelihood of reversion increased by 1.95-fold (OR 1·95; 95% CI 1·22-3·15, p = 0·0053) among individuals with a decrease in TG of ≥ 25%. Adjusted ORs and 95% CIs for OH and euthyroidism outcome according to other categorical longitudinal changes in TG are shown in Supplemental Table 2.

Subgroup and sensitivity analysis

Subgroup analyses by baseline levels of TC and TG showed similar associations between the percent changes in TC and TG levels and the outcome of OH (Figure 3A and C). Interestingly, the pattern of associations was more prominent when the baseline TC level was high (OR 19·5; 95% CI 1·04-33·72, p = 0·047). In individuals with high levels of TC and TG at baseline, a decrease in TC (OR 4·46; 95% CI 1·25-19·59, p = 0·030) and TG (OR 2·99; 95% CI 1·31-7·09, p = 0·011) both increases the likelihood of returning to euthyroidism. However, changes in TC and TG levels were not significantly associated with the likelihood of reversion when the baseline TC and TG levels were normal (Figure 3B and D).

The results remained similar when excluding individuals taking lipid-lowering drugs from the dataset (Supplemental Table 3 and Supplemental Table 4). Additionally, the main findings did not change significantly after further adjustment for SBP, ALT, and HbA1c and at baseline (Supplemental Table 5 and Supplemental Table 6).

Cohort of replication

A total of 412 individuals with SCH were included in the validation cohort. The characteristics of the study's population are summarized in Supplemental Table 7. Over a median follow-up of two [IQR,1·92-2·08] years, 156 (37·9%), 228 (55·3%), and 23 (5·6%) individuals had regression to euthyroidism, persistent SCH, and progression to OH, respectively. Serum TC and TG levels increased in individuals who progressed to OH (ΔTC = 0·50 mmol/L, ΔTG = 0·08 mmol/L), but decreased in individuals with euthyroidism (ΔTC = −0·05 mmol/L, ΔTG = −0·07 mmol/L) (Supplemental Table 8 and Supplemental Table 9). With increasing

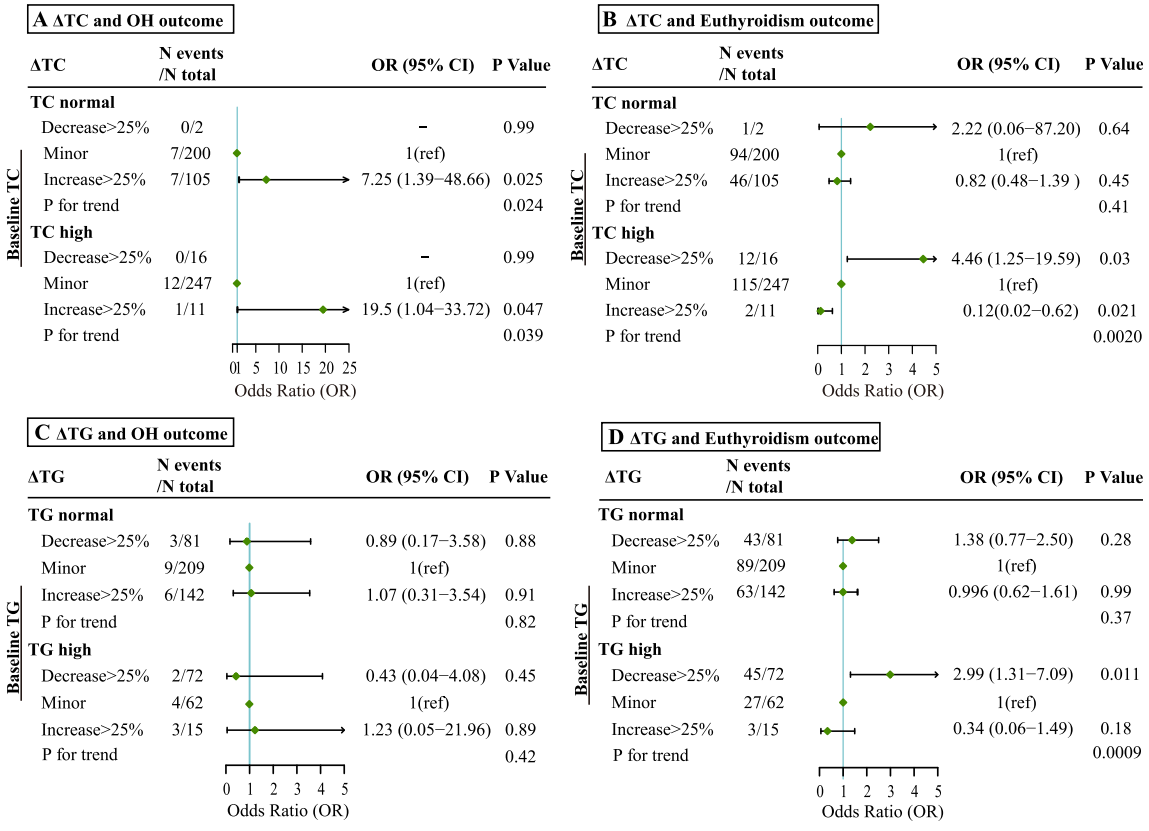

Figure 3. Adjusted ORs and 95% CIs for OH and euthyroidism outcome according to baseline TC and TG levels. ORs (95% CIs) were adjusted for age, sex, BMI, TSH, FT3, FT4, TPOAb, Cr, smoking, and drinking at baseline. (A) Adjusted ORs and 95% CIs for OH outcome according to baseline TC levels. (B) Adjusted ORs and 95% CIs for euthyroidism outcome according to baseline TC levels. (C) Adjusted ORs and 95% CIs for OH outcome according to baseline TG levels. (D) Adjusted ORs and 95% CIs for euthyroidism outcome according to baseline TG levels. Abbreviations: TC, total cholesterol; TG, triglyceride; OH, overt hypothyroidism; OR, odds ratio; 95% CI, 95% confidence interval.

	OH				Euthyroidism			
	N total	N event (%)	OR (95%CI)	*P* value	N total	N event (%)	OR (95%CI)	*P* value
Per unit increase in ΔTC			1.58 (1.02-2.38)	0.028			0.75 (0.57-0.96)	0.034
Tertile range of ΔTC								
Q1 (< −0.20 mmol/L)	138	4 (2.9%)	1 (ref)		138	60 (43.5%)	1 (ref)	
Q2 (−0.20—0.33mmol/L)	138	6 (4.3%)	1.39 (0.33-6.34)	0.65	138	56 (40.6%)	0.74 (0.44-1.25)	0.26
Q3 (> 0.33 mmol/L)	136	13 (9.6%)	3.89 (1.13-16.35)	0.042	136	40 (29.4%)	0.40 (0.23-0.70)	0.001
P for trend				0.028				0.001
Percentage of ΔTC								
Decrease >25%	21	0 (0%)	-	-	21	11 (52.4%)	2.92 (1.05-8.33)	0.040
Minor (decrease <25% to increase >25%)	371	20 (5.4%)	1 (ref)		371	143 (38.5%)	1 (ref)	
Increase >25%	20	3 (15.0%)	4.80 (0.74-26.04)	0.077	20	2 (10.0%)	0.17 (0.03-0.65)	0.024
P for trend				-				0.002

***Table 4*: Adjusted ORs and 95% CIs for OH and euthyroidism outcome according to longitudinal changes in TC levels in validation cohort.**
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; OH, overt hypothyroidism; ΔTC = TC concentration at the second visit − TC concentration at the first visit; Q1, Q2, and Q3 represent the first, second, and third tertile of ΔTC; Percentage of ΔTC = ΔTC / TC concentration at the first visit*100; -, none of the participants.
ORs (95% CIs) were adjusted for age, sex, BMI, TSH, FT_3, FT_4, TPOAb, Cr, smoking, drinking, TC, and TG at baseline.

	OH				Euthyroidism			
	N total	N event (%)	OR (95%CI)	*P* value	N total	N event (%)	OR (95%CI)	*P* value
Per unit increase in ΔTG			1.11 (0.63-1.51)	0.56			0.65 (0.43-0.94)	0.032
Tertile range of ΔTG								
Q1 (< −0.21 mmol/L)	138	5 (3.6%)	1 (ref)		138	65 (47.1%)	1 (ref)	
Q2 (−0.21—0.19 mmol/L)	138	7 (5.1%)	1.73 (0.43-7.43)	0.44	138	50 (36.2%)	0.59 (0.33-1.03)	0.064
Q3 (> 0.19 mmol/L)	136	11 (8.1%)	2.56 (0.74-10.00)	0.15	136	41 (30.1%)	0.43 (0.24-0.75)	0.0036
P for trend				0.15				0.0040
Percentage of ΔTG								
Decrease >25%	89	2 (2.2%)	0.43 (0.06-2.00)	0.33	89	45 (50.6%)	1.72 (1.00-2.97)	0.049
Minor (decrease <25% to increase >25%)	209	12 (5.7%)	1 (ref)		209	77 (36.8%)	1 (ref)	
Increase >25%	114	9 (7.9%)	1.81 (0.57-5.80)	0.31	114	34 (29.8%)	0.67 (0.40-1.13)	0.14
P for trend				0.098				0.0045

***Table 5*: Adjusted ORs and 95% CIs for OH and euthyroidism outcome according to longitudinal changes in TG levels in validation cohort.**
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; OH, overt hypothyroidism; ΔTG = TG concentration at the second visit − TG concentration at the first visit; Q1, Q2, and Q3 represent the first, second, and third tertile of ΔTG. Percentage of ΔTG = ΔTG / TG concentration at the first visit *100.
ORs (95% CIs) were adjusted for age, sex, BMI, TSH, FT_3, FT_4, TPOAb, Cr, smoking, drinking, TC, and TG at baseline.

tertiles of ΔTC and ΔTG, the incidence of OH increased, and the incidence of regression to euthyroidism decreased significantly (Tables 4 and 5). Multiple logistic regression showed that individuals with an increase in TC of ≥25% has a trend towards a high risk of progression to OH. Correspondingly, a decrease in TC and TG of ≥25% has a trend towards a high likelihood of regression to euthyroidism (Tables 4 and 5).

Discussion

In the present study, we first investigated whether long-term dynamic changes in serum lipids were associated with the natural history of SCH in a community-based population. The results suggested that 3-year changes in serum lipids were related to the natural history of SCH. Specifically, a dynamic increase in TC levels increased the risk of developing OH, while a dynamic decrease in TC and TG levels was associated with a higher likelihood of regression to euthyroidism. Importantly, these findings were confirmed in the validation cohort. Collectively, our results indicated that clinical changes in TC and TG levels—either an increase or a decrease—may give rise to corresponding changes in the risk of future progression or reversion in people with SCH.

It is widely accepted that patients with OH and SCH are prone to dyslipidaemia. Dyslipidaemia is a serious public health problem worldwide.[19] Lipotoxicity has

attracted worldwide attention because of its extensive and serious harm to human health.[20] Recently, Song et al. noted that excess cholesterol-induced toxicity is ubiquitous, which means that the excessive accumulation of cholesterol in various tissues and organs plays a crucial role in the pathogenesis of many diseases.[13] However, to date, few studies have focused on the effect of serum lipids on thyroid function. Two population-based studies revealed that TG is a risk factor for SCH.[12,21] Li et al. also found that high TC levels at baseline increased the risk of progression to OH in patients with mild SCH.[22] In our study population, we observed no difference in baseline lipid levels among the euthyroidism, SCH, and OH groups. Nevertheless, the tissue damage caused by dyslipidaemia is a long-term and chronic process. Therefore, it is not entirely reasonable to predict the course of SCH only using baseline serum lipid measurements; dynamic changes should also be evaluated. To our knowledge, this is the first study to explore the relationship between longitudinal changes in serum lipids and the natural history of SCH in community-based populations and revealed that longitudinal changes in serum lipids are important factors influencing the course of SCH. We provide new evidence to support the hypothesis that lipid metabolism disorders may lead to thyroid dysfunction. These findings could have important implications for clinical practice and may be valuable in guiding clinical management strategies for SCH.

Although conclusions regarding causality must be interpreted with caution due to the nature of observational studies, increasing evidence has indicated that lipid metabolism disorders might play roles in the pathogenesis of thyroid dysfunction. For TC, we found that the increase in TC levels increased the risk of progression to OH, while the decrease increased the probability of regression to euthyroidism, which indicates the adverse effect of TC on thyroid function. Several recent population studies have provided support for our findings. It was reported that high TC levels at baseline increased the risk of progression to OH in patients with mild SCH.[22] A retrospective cohort study found that statin use was associated with benefits for thyroid function, and TC served as a mediator of the association between statin use and TSH levels.[15] Endoplasmic reticulum (ER) stress may be one of the potential mechanisms of cholesterol-induced hypothyroidism.[23–26] The accumulation of too much cholesterol can cause ER stress,[23,24] which contributes to the occurrence of hypothyroidism.[25] One likely explanation is that ER stress can attenuate the expression of key genes involved in thyroid hormone synthesis in thyrocytes.[26] In our experimental rat model, we found the expression of two important cholesterol receptors, Niemann-Pick C1-like1 (NPC1L1) and LDL receptor, in the thyroid of SD rats and observed that a high-cholesterol diet could affect thyroid function by inducing ER stress (data not shown). In addition, by interacting with oxysterol-binding protein outside of the membrane, cholesterol controls the signal-regulated kinase (ERK) signalling pathway,[27] which represses the function of thyroid transcription factor-1 (TTF-1). TTF-1 is critically involved in the transcriptional regulation of the expression of key thyroid hormone synthesis-related molecules.[28]

Due to the relatively small sample size, the relationship between changes in TG levels and the progression to OH did not reach statistical significance, but there was still a correlation trend between them. Therefore, we cannot absolutely conclude that the changes in TG levels were completely unrelated to the progression to OH. Moreover, in this study, we found that the decrease in TG levels was conducive to the conversion of SCH to euthyroidism. Indeed, evidence from some of our other studies suggests an effect of TG on thyroid function.[12,29] We previously conducted a case–control study and reported a higher risk of SCH in individuals with hypertriglyceridaemia, even after adjustment for potential confounders.[12] In a prospective cohort study of 66,822 individuals, patients with high TG levels were at a 21% excess risk of developing SCH.[21] Additionally, rats fed a high-fat diet also showed a decrease in the levels of TT4 and FT4 and an increase in the level of TSH, which are characteristics of hypothyroidism.[29] We studied the mechanism and found that the expression of key molecules, including thyroglobulin, sodium iodide symporter, and thyroperoxidase, in thyroid hormone synthesis decreased under the stimulation of palmitic acid, the most abundant saturated fatty acid found in the bloodstream.[30] Further studies proved that this phenomenon was mediated by ER stress caused by a high-fat diet.[25] Hence, ER stress could also be a potential mechanism connecting TG levels and thyroid function.

Since no patients experienced a decrease in TC of $\geq$ 25%, we could not observe the relationship between the decrease in TC levels and progression to OH. In subgroup analysis, we observed that the relationship between the increase in TC levels and progression to OH was stronger in individuals with hypercholesterolemia at baseline, and the relationship between the decrease in TC and TG levels and reversion was only observed in the group with high levels at baseline, indicating that we should pay more attention to these people when we choose who should be treated for dyslipidaemia. The reason for this result may also be the fact of the so-called regression to the mean. This leads to fewer people with high baseline lipid levels that subsequently increase or low baseline lipid levels that subsequently decrease, which might result in insufficient statistical power, and the results should be interpreted with caution.

The major strengths of this study include the following: 1) This study is the first to examine the associations between the longitudinal statuses of serum lipids and the natural history of SCH, and focused on the long-term dynamic changes in serum lipids to avoid the

contingency of a single observation. We innovatively found that the long-term dynamic changes in serum lipids were factors that may influence the natural history of SCH. 2) The assessment of the relationship between changes in TC and TG levels and the natural history of SCH was based on multiple approaches, including different grouping methods for evaluating changes in TC and TG levels, which improved the reliability of the conclusions. 3) Our findings have potential significance for clinical practice and may be valuable for guiding the management strategy of hypothyroidism. Nevertheless, certain potential limitations also exist. First, the sample size was relatively small, which might have reduced the statistical power. Although we performed subgroup and sensitivity analyses to assess the robustness of our results and found similar results, which means that our results are credible to some extent, these findings are necessary to be replicated in larger samples. Second, thyroid function was defined based on a single thyroid function test. As serum TSH concentrations can elevate transiently, some individuals may have been misclassified. In an epidemiologic study, it is usually acceptable to use diagnosis based on a single thyroid function test considering the difficulty in practice.[31]

In conclusion, dynamic changes in serum lipid levels are associated with the natural history of SCH. A dynamic increase in TC levels increases the risk of progression to OH, while a dynamic decrease in TC and TG levels is associated with a higher likelihood of regression to euthyroidism. The obtained results provide some evidence that changes in TC and TG levels may have important prognostic utility for the population with SCH. More emphatically, the long-term control of TC and TG levels, such as through weight loss and some pharmacological interventions, may benefit thyroid function in populations with SCH. The results also may have implications for the role of serum lipids in the aetiology of hypothyroidism. More studies are required to further clarify the underlying mechanisms of the effect of serum lipids on thyroid function.

Contributors

Study concept and design: Z.F, Z.M, Z.J.
Data collection: G.Q, Z.H, Z.X.
Data analysis: Z.F.
Data access and verify: Z.J, Y.Z, W.Z.
Data interpretation: Z.F, Z.M, L.Q, W.Z.
Manuscript drafting: Z.F,
Critical review of manuscript for content: Y.Z, F.X, H.J, L.Q, W.Z, S.S.
Obtained funding: Z.J.

Data sharing statement

All statistical outputs in the present study are included in the main text or the supplementary files. Further enquiries could be sent to the corresponding author.

Declaration of interests

All authors declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101629.

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