Exploring the Association between Thyroid Function and Frailty: Insights from Representative Korean Data

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Background: This study investigates the association between thyroid function and frailty in the old patients using representative data.
Methods: The study was conducted using data from the Korea National Health and Nutrition Examination Survey conducted from 2013 to 2015. The study population included 2,416 participants aged 50 years and older with available thyroid function test data. Frailty assessment was performed using the Fried frailty phenotype. The prevalence of frailty was analyzed across different thyroid diseases and thyroid function parameters.
Results: The significant association between thyroid dysfunction and frailty was observed in overt hyperthyroidism and subclinical hyperthyroidism. After adjusting for various factors, the association between thyroid dysfunction and frailty remained significant. On the other hand, overt hypothyroidism did not show a significant association with frailty in the adjusted analysis. For individuals with overt hyperthyroidism and subclinical hyperthyroidism, higher levels of free thyroxine (FT4) were significantly associated with an increased risk of frailty (aOR >999; 95% CI, >999 to 999). Among individuals with overt hypothyroidism, lower level of FT4 levels and high thyrotropin (TSH) levels showed a significant association with frailty risk (FT4: aOR, <0.01; TSH: aOR, 999). In participants with subclinical hypothyroidism, there were no significant associations between parameters for thyroid and frailty risk.
Conclusion: These findings suggest that thyroid dysfunction, particularly overt hyperthyroidism and subclinical hyperthyroidism, may be associated with an increased risk of frailty in the old patients.

Keywords: Frailty; Thyroid; Thyroid function tests; Aged

INTRODUCTION

With the global population of older adults on the rise, the condition of frailty has garnered increasing international attention. Fried et al. [1] conceptualized frailty as a clinical syndrome characterized by a specific physical phenotype, particularly demonstrating its effectiveness. Frailty is defined as a multidimensional syndrome characterized by vulnerability to stressors and a decreased ability to recover from stressors [2]. Frailty, although separate from comorbidity or disability, is increasingly acknowledged as a distinct phenotype due to growing evidence. Notably, frailty is not limited to specific age groups but can be observed throughout adulthood. However, it is important to highlight that frailty is closely associated with aging, and its prevalence tends

to rise as the population ages. Frailty is widely recognized as a significant global health burden characterized by an increased risk of short-term mortality as well as other adverse outcomes such as falls, fracture, disability, and hospitalization [3]. According to a systematic review, the prevalence of frailty has been reported to be from 4% to 59.1% [4]. Another study reported that pooled frailty was 17.4% [5]. In Korea, the prevalence of frailty among people aged 70 to 80 years was 7.8% according to the Korean Frailty and Aging Cohort Study [6]. Thus, the prevalence of frailty can vary significantly across different populations, and no global estimate of frailty prevalence has been established. One of the main reasons for this variation is the use of different definitions and criteria for assessing frailty. No gold standard has been established to assess frailty. The frailty index (FI) and the Fried frailty phenotype (FFP) are commonly used in clinical practice and have been well-validated in many population-based studies [7]. The FFP model defines frailty as the combined presence of weight loss, weakness, exhaustion, slow gait, and low physical activity (PA) [1].

Thyroid dysfunction has wide-ranging effects on various aspects of health, including glucose and lipid metabolism, musculoskeletal function, cognition, and the cardiopulmonary system. Age-related changes in thyroid hormone concentrations, characterized by increased thyrotropin (TSH) levels, decreased free triiodothyronine levels, and stable free thyroxine (FT4) levels, further underscore the significance of thyroid function [8]. The relationship between thyroid dysfunction and frailty has not been fully elucidated in well-defined frail cohorts. Therefore, our objective in this study was to investigate the association between thyroid function and frailty using utilizing the well-validated FFP tool for assessing frailty, along with representative data from Korea.

METHODS

Study population and data collection

This population-based cohort study analyzed data from the Korea National Health and Nutrition Examination Survey (KNHANES) conducted during KNHANES VI from 2013 to 2015. KNHANES is a dataset collected by the Korean Centers for Disease Control and Prevention for Health Statistics. It monitors the health and nutritional status of the Korean population, and assessments are conducted by trained interviewers. The survey uses a stratified multistage probability sampling design to select participants and ensure representativeness across the entire South Korean population. The selection process involves a two-stage stratified system-

atic sampling method that accounts for various demographic and geographic factors when choosing participants. More specific information about the KNHANES database, including its contents and methodology, can be found at https://knhanes.cdc.go.kr. This study adhered to the ethical standards outlined in the Declaration of Helsinki, and we obtained approval from the Catholic University of Korea, Catholic Medical Center, Eunpyeong St. Mary's Hospital Institutional Review Board (IRB approval No. PC23ZI-SI0101). Because we analyzed previously collected and anonymized data, the need for written informed consent was waived. In total, 26,032 people participated in KNHANES VI from 2013 to 2015; among them, 2,374 were older than 50 years and had available thyroid function test (TFT) data.

Laboratory analyses

All blood samples were obtained in the morning following an 8-hour fasting period. The samples were promptly processed, centrifuged, aliquoted, and sent to the Central Testing Institute in Seoul, Korea, for analysis within 24 hours. Serum levels of TSH, FT4, and thyroid peroxidase antibody (TPOAb) were measured using an electrochemiluminescence immunoassay with specific kits (E-TSH kit, E-Free T4 kit, and E-Anti-TPO kit) from Roche Diagnostics, Mannheim, Germany. Spot urine samples were collected under fasting conditions, with the first morning midstream urine being obtained from most of the study population. Urine iodine concentration (UIC) was determined using inductively coupled plasma mass spectrometry with an iodine standard (Inorganic Venture, Christiansburg, VA, USA). To account for renal function limitations and adjust for water excretion rates at the time of spot urine collection, the UIC to creatinine ratio (μg [iodine]/g [creatinine]) was calculated. The reference range for FT4 was 0.89 to 1.76 ng/mL, and that for TSH was 0.35 to 5.50 mIU/L. However, considering the influence of iodine intake on TSH levels and the high prevalence of excessive iodine levels in Korea [9], the reference range for TSH was adjusted to 0.62 to 6.68 mIU/L based on population data [10]. The reference range for TPOAb was 0 to 34 IU/mL. Overt hypothyroidism was defined as FT4 <0.89 ng/mL and TSH >6.67 mIU/L. Overt hyperthyroidism was defined as FT4 >1.76 ng/mL and TSH <0.62 mIU/L. Subclinical hyperthyroidism and subclinical hypothyroidism were defined with normal FT4 levels and TSH <0.62 mIU/L or TSH >6.67 mIU/L, respectively.

Demographic variables and lifestyle factors

Demographic and lifestyle information about the participants

was collected through a questionnaire. Smoking status was categorized into three groups: never smokers (adults who never smoked or smoked fewer than 100 cigarettes in their lifetime), former smokers (individuals who smoked more than 100 cigarettes in their lifetime but had quit at the time of the survey), and current smokers (those who had smoked more than or equal to 100 cigarettes in their lifetime and were still smoking at the time of the survey). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m²). Risky drinking was defined as consuming at least 210 g of alcohol per week for males and 140 g of alcohol per week for females. PA was assessed using the validated Korean version of the International Physical Activity Questionnaire Short-Form (IPAQ-SF) [11]. PA was quantified as metabolic equivalents based on the duration (in minutes) of vigorous aerobic PA, moderate aerobic PA, and walking per week, using the scoring protocol of the IPAQ [12]. Self-reported health was classified as poor or very poor, moderate, and good or very good.

Assessment of frailty

Our primary focus was on assessing frailty using the FFP. The FFP considers five binary criteria: (1) shrinking, (2) low PA, (3) weakness, (4) exhaustion, and (5) slowness. These criteria are used to evaluate and classify the frailty status of individuals [1]. It is worth mentioning that in the KNHANES, participants were guided to choose responses from a predefined set of options regarding weight loss in the second survey question. Consequently, we were unable to use the specific cut-off point of the FFP, which requires an unintentional weight loss of more than 10 pounds in the previous year. Instead, we defined unintentional weight loss as a loss of 6.61 pounds, which deviates from the FFP criteria. This decision was based on the settings used in a previous study conducted using KNHANES data [13]. Low PA was defined as the lowest 20%, in accordance with the FFP definition. Weakness was evaluated using handgrip strength (HGS), which was measured with a digital grip strength dynamometer (TKK 5401, Takei Scientific Instruments Co. Ltd., Tokyo, Japan). HGS was measured while subjects were in a standing position. Starting with the dominant hand and alternating, each hand was tested three times. The average HGS value of the dominant hand was used as the final HGS, according to a consensus from the Asian Working Group of Sarcopenia [14]. Weakness was defined as being in the lowest 20% of HGS values. Exhaustion was evaluated by responses to a question in the health interviews that asked, "How often in the past week did you feel that everything you did was an effort?" Slowness was evaluated based on

self-reported walking disability due to the lack of gait speed data in the KNHANES. The selected question from the EuroQol-5 Dimension Questionnaire asked whether the respondent had a problem walking about or was confined to bed. In the FFP, total frailty scores range from 0 to 5. In this study, frailty status was classified into three groups: robust (0), prefrail (1–2), and frail (3–5).

Statistical analysis

Statistical analysis was performed to reflect the complex sampling design and sampling weights used in KNHANES to provide nationally representative prevalence estimates. The SAS PROC SURVEY module was used to consider the strata, clusters, and weights. Demographic variables (sex, smoking status, drinking behavior, marital status, educational status, income level, PA, and self-perceived stress) were analyzed by a complex sample analysis using the Rao-Scott chi-squared test. The characteristics of each group were compared using independent t tests for continuous variables. Based on the data characteristics, the results are expressed as mean±standard error, geometric means (95% confidence interval [CI]), or percentages, as appropriate. percentages. The use of the geometric mean is appropriate for skewed data and provides a more accurate representation of the central tendency of the TSH distribution. The logistic regression analysis used a multivariate analysis to test the associations between frailty and risk factors in a complex sampling design. The logistic regression was used to calculate odds ratios (ORs) with 95% CIs for frailty. A $P<0.05$ was considered to be statistically significant.

RESULTS

Characteristics of the study participants

Table 1 presents the demographic and clinical characteristics of the 2,374 participants, stratified according to their frailty status. Most participants aged 50 to 59 years were robust (54.6%), followed by the prefrail (40.4%) and frail (42.9%) groups. In the 60 to 69 age group, the prevalence of frailty increased, with robust individuals accounting for 42.0%, prefrail individuals accounting for 52.5%, and frail individuals accounting for 50.0%. In the population aged 70 years and above, the prevalence of pre-frailty was found to be the highest (7.4%) compared with the other age groups, and this difference was statistically significant ($P<0.001$). In the frailty groups, females were predominant (100% female). BMI showed increase trend according to frailty (BMI robust, prefrail, and frail group: 24.2±3.0, 24.6±3.3, and

Table 1. Baseline Clinical Characteristics of the Subjects (Unweighted)

Clinical parameter	Total (n=2,374)	Robust (n=1,667)	Prefrail (n=693)	Frail (n=14)	P value
Age, yr					<0.001
50–59	1,196 (50.4)	910 (54.6)	280 (40.4)	6 (42.9)	
60–69	1,069 (45.0)	700 (42.0)	362 (52.2)	7 (50.0)	
≥70	109 (4.6)	57 (3.4)	51 (7.4)	1 (7.1)	
Male sex	1,172 (49.4)	942 (56.5)	230 (33.2)	0	<0.001
BMI, kg/m²	24.3±3.1	24.2±3.0	24.6±3.3	25.1±5.1	0.120
Smoking status					<0.001
Never smoker	1,297 (56.1)	833 (51.7)	453 (66.1)	11 (78.6)	
Ex-smoker	568 (24.6)	456 (28.3)	111 (16.2)	1 (7.1)	
Current smoker	446 (19.3)	323 (20.0)	121 (17.7)	2 (14.3)	
Risky drinking	232 (9.8)	192 (16.8)	40 (9.8)	0	0.002
Education	232 (15.0)				0.001
High school or less	70 (6.2)	28 (4.3)	39 (8.4)	3 (21.4)	
More than high school	1,064 (93.8)	625 (95.7)	428 (91.7)	11 (78.6)	
Income					<0.001
Low	497 (21.3)	264 (15.9)	224 (32.5)	9 (64.3)	
Middle	1,270 (56.6)	905 (54.6)	361 (52.3)	4 (28.6)	
High	596 (25.1)	490 (29.5)	105 (15.2)	1 (7.1)	
Living alone	484 (20.4)	287 (17.2)	191 (27.6)	6 (42.9)	<0.001
Self-reported health					<0.001
Poor or very poor	509 (22.8)	215 (14.0)	283 (41.2)	11 (78.6)	
Moderate	1,146 (51.3)	832 (54.2)	311 (45.3)	3 (21.4)	
Good or very good	581 (25.9)	488 (31.8)	93 (13.5)	0	
No. of comorbidities					0.240
<2	1,753 (74.5)	1,242 (75.4)	500 (72.2)	11 (78.6)	
More than 2	601 (25.5)	405 (24.6)	193 (27.9)	3 (21.4)	
FT4, ng/dL	1.2±0.3	1.2±0.2	1.2±0.3	1.1±0.2	0.137
TSH, μIU/mL[a]	2.2±2.4	2.2±0.1	2.1±0.1	1.6±0.5	0.814
TPOAb, IU/mL	45.4±234.1	42.4±233.8	52.3±236.1	64.33±169.4	0.280
Urine iodine, μg/creatinine g	873.3±2,495.6	891.2±2,071.9	800.8±3,218.2	2,323.4±5,494.6	<0.001

Values are expressed as number (%) or mean±standard error.
BMI, body mass index; FT4, free thyroxine; TSH, thyrotropin; TPOAb, thyroid peroxidase antibody.
[a]Geometric mean±standard error, P value for log-transformed variable.

25.1±5.1 kg/m²). However, no significant differences in BMI were observed.

Significant differences were observed in the habitual factors of smoking and risky drinking among the three groups. The robust group demonstrated the highest prevalence of current smoking and risky drinking. Additionally, individuals in the robust group had a higher education status compared to both the prefrail and frail groups. the self-reported health response was significantly poorest in the frail group compared to the prefrail

and robust groups. The prevalence of comorbidities did not significantly differ across the group. In the TFT, there was no significant difference in the FT4, TPOAb, or UIC levels among the three groups.

The prevalence of frailty according to thyroid disease

Table 2 shows the prevalence of frailty according to thyroid disease. The data include both unweighted and weighted frequencies to ensure accurate representation of the population. In the

Table 2. The Prevalence of Frailty according to Thyroid Disease

Clinical parameters	Robust	Prefrail	Frail	P value
Unweighted frequency				0.092
Overt hypothyroidism	21 (1.3)	5 (0.7)	0	
Overt hyperthyroidism	7 (0.4)	10 (1.5)	0	
Euthyroidism	1,497 (92.5)	602 (91.1)	12 (92.3)	
Subclinical hyperthyroidism	67 (4.1)	34 (5.1)	0	
Subclinical hypothyroidism	26 (1.6)	10 (1.5)	1 (7.7)	
Weighted frequency				<0.001
Overt hypothyroidism	150,664 (1.6)	25,349 (0.7)	0	
Overt hyperthyroidism	33,050.92 (0.3)	54,989.55 (1.5)	0	
Euthyroidism	9,014,418 (92.7)	3,318,112 (89.3)	43,038 (88.3)	
Subclinical hyperthyroidism	375,165 (3.9)	245,594 (6.6)	0	
Subclinical hypothyroidism	151,495 (1.6)	70,360.91 (1.9)	5,692 (11.7)	

Values are expressed as number (%).

Table 3. Cross-Sectional Relationship between Thyroid Function and Frailty

Thyroid disease	Odds ratio (95% confidence interval)			
	Model 1	Model 2	Model 3	Model 4
Overt hypothyroidism	0.42 (0.14–1.27)	0.35 (0.09–1.37)	0.37 (0.10–1.42)	0.37 (0.10–1.44)
Overt hyperthyroidism	4.42 (1.60–12.23)[a]	3.72 (1.04–13.33)[a]	3.91 (1.03–14.93)[a]	3.74 (0.96–14.56)
Subclinical hyperthyroidism	1.70 (1.07–2.70)[a]	1.76 (0.95–3.26)	2.06 (1.11–3.82)[a]	2.06 (1.11–3.82)[a]
Subclinical hypothyroidism	1.07 (0.42–2.73)	0.50 (0.10–2.45)	0.48 (0.10–2.38)	0.48 (0.10–2.38)

Model 1: adjustment for age and sex; Model 2: model 1+body mass index, smoking, and drinking; Model 3: model 2+urine iodine; Model 4: model 3+comorbidities.

[a]Statistical significance with a $P<0.05$.

unweighted analysis, no significant differences were observed in the prevalence of frailty across the thyroid disease categories ($P=0.092$). In the weighted frequency analysis, the prevalence of frailty based on the FFP assessment showed significant differences ($P<0.001$). The majority of participants fall under the euthyroidism category, with 92.5% classified as robust, 91.1% as prefrail, and 92.3% as frail. Among those with thyroid disease, individuals with overt hypothyroidism and overt hyperthyroidism have the lowest prevalence of frailty, while those with subclinical hypothyroidism have the highest prevalence of frailty. Among participants with overt hypothyroidism, the percentage of robust individuals is 1.3%, prefrail is 0.7%, and no individuals are classified as frail. For subclinical hypothyroidism, the percentage of robust individuals is 1.6%, prefrail is 1.5%, and the prevalence of frailty is notably higher at 7.7%.

Association between thyroid disease and frailty

According to FFP assessment, overt hyperthyroidism initially displayed a significant positive association with frailty, with an OR of 4.42 (95% CI, 1.60 to 12.23) observed in the crude model, model 2, and model 3. However, after adjusting for multiple factors, the association was no longer significant. On the other hand, subclinical hyperthyroidism exhibited a significant positive association with frailty across the models, with increasing OR ranging from 1.70 to 2.06, indicating a consistent and significant association between subclinical hyperthyroidism and frailty (Table 3).

Association between thyroid hormone parameters and frailty

As shown in the adjusted regression analysis presented in Table 4, no significant associations were found between thyroid hor-

Table 4. Associations between Thyroid Hormone Parameters and Frailty

Thyroid hormone	Odds ratio (95% confidence interval)			
	Model 1	Model 2	Model 3	Model 4
FT4	1.28 (0.81–2.02)	1.93 (0.89–4.19)	1.88 (0.86–4.14)	1.87 (0.85–4.10)
TSH	0.94 (0.83–1.07)	1.05 (0.90–1.23)	1.06 (0.90–1.24)	1.06 (0.90–1.24)
TPOAb	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)

Model 1: adjustment for age and sex; Model 2: model 1+body mass index, smoking, and drinking; Model 3: model 2+urine iodine; Model 4: model 3+comorbidities.
FT4, free thyroxine; TSH, thyrotropin; TPOAb, thyroid peroxidase antibody.

Table 5. Associations between Thyroid Hormone Parameters and Frailty according to Thyroid Disease

Thyroid hormone	Odds ratio (95% confidence interval)			
	Model 1	Model 2	Model 3	Model 4
Overt hypothyroidism				
FT4	<0.01 (<0.01->999)	<0.01 (<0.01–<0.01)[a]	<0.01 (<0.01–<0.01)[a]	<0.01 (<0.01–<0.01)[a]
TSH	0.20 (0.00–10.88)	>999 (>999->999)[a]	>999 (>999->999)[a]	>999 (>999->999)[a]
TPOAb	1.00 (1.00–1.00)	1.00 (1.00–1.00)	0.99 (0.99–1.00)	0.99 (0.99–0.99)[a]
Overt hyperthyroidism				
FT4	1.09 (0.45–2.62)	>999 (>999->999)[a]	>999 (>999->999)[a]	>999 (>999->999)[a]
TSH	>999 (>999->999)[a]	>999 (>999->999)[a]	>999 (>999->999)[a]	>999 (>999->999)[a]
TPOAb	1.00 (1.00–1.01)	0.96 (0.94–0.98)[a]	1.00 (0.98–1.02)	1.12 (1.10–1.14)[a]
Subclinical hypothyroidism				
FT4	9.24 (0.39–221.44)	139.89 (0.58->999)	60.44 (0.20->999)	60.82 (0.21->999)
TSH	0.15 (0.02–1.32)	0.15 (0.01–2.43)	0.16 (0.01–2.63)	0.16 (0.01–2.62)
TPOAb	1.00 (1.00–1.00)	1.00 (1.00–1.01)	1.00 (1.00–1.01)	1.00 (1.00–1.01)
Subclinical hyperthyroidism				
FT4	0.29 (0.01–11.28)	0.02 (<0.01–3.53)	0.01 (<0.01–1.05)	>999 (247.35->999)[a]
TSH	0.48 (0.22–1.05)	<0.01 (<0.01–<0.01)[a]	<0.01 (<0.01–<0.01)[a]	<0.01 (<0.01–<0.01)[a]
TPOAb	1.00 (1.00–1.00)	0.98 (0.98–0.99)[a]	0.98 (0.97–0.98)[a]	0.95 (0.95–0.96)[a]

Model 1: adjustment for age and sex; Model 2: model 1+body mass index, smoking, and drinking; Model 3: model 2+urine iodine; Model 4: model 3+comorbidities.
FT4, free thyroxine; TSH, thyrotropin; TPOAb, thyroid peroxidase antibody.
[a]Statistical significance with a $P<0.05$.

mone parameters and frailty. Although there was a positive correlation observed between FT4 and frailty, it did not reach statistical significance. The associations between thyroid hormone parameters and frailty were further examined by stratifying individuals based on different thyroid diseases, as shown in Table 5. FT4 showed a highly significant negative association with frailty among individuals with overt hypothyroidism across all models, with very low ORs. TSH had a significant association and a high OR (>999; 95% CI, >999 to >999), except in model 1 where it showed a negative association (OR, 0.20; 95% CI, 0.00 to 10.88). In individuals with overt hyperthyroidism, FT4

and TSH were the risk factors for frailty in the adjusted model. The presence of TPOAb was significantly associated with increased frailty risk in the adjusted models in overt hyperthyroidism (adjusted odds ratio [aOR], 1.12; 95% CI, 1.10 to 1.14). For subclinical hypothyroidism, FT4, TSH, and TPOAb did not exhibit a significant association with frailty in any of the models. However, FT4 was positively associated with frailty (aOR >999) and TSH was negatively correlated with frailty in subclinical hyperthyroidism (aOR <0.001). TPOAb was significantly associated with increase in the risk of frailty in overt hyperthyroidism. In contrast, TPOAb showed decreased frailty

risk in the adjusted models in overt hypothyroidism and subclinical hyperthyroidism group.

DISCUSSION

In this study, we explored the association between thyroid function/thyroid disease and frailty based on the well-established tools widely used to assess frailty. First, we observed that the prevalence of frailty differed according to age group, with the highest prevalence observed in individuals aged 60 to 69 years. Additionally, females were more likely than males to be classified as frail, particularly using the FFP criteria. Regarding the association between thyroid disease and frailty, our results show that overt hyperthyroidism was significantly positively associated with frailty. When we examined the association between thyroid hormone parameters and frailty, no significant associations were found in this FFP model. Subgroup analyses stratified by thyroid diseases revealed varied associations between thyroid hormone parameters and frailty depending on the specific condition and assessment tool used.

In this study, we used a representative dataset and investigated the prevalence of frailty among participants older than 50 years. Most individuals in that age group, 55.0% of the population, were categorized as prefrail or frail. The prevalence of prefrailty was higher than that of frailty in both the 60–69 and ≥70 age groups. This discrepancy suggests that the choice of assessment tool can influence the classification of individuals into frailty categories. In previous studies, the prevalence of frailty using the FI has been reported to be higher than that using the FFP [15,16]. The cumulative FI, which uses a checklist of clinical illnesses, has been established as a more sensitive tool, and the FFP is the most widely used tool [17]. Therefore, when choosing an appropriate frailty instrument, it is crucial to consider the intended purpose. Another factor that could contribute to the different prevalence rates observed is differences in age selection. In this study, we analyzed participants older than 50 years because the proportion of individuals older than 70 years in the KNHANES dataset is relatively small.

Our study provides valuable insights into the relationship between thyroid dysfunction and frailty, with a particular focus on different thyroid diseases. One significant finding is the strong association between overt hyperthyroidism and frailty, as evidenced by the four-fold increased risk observed. Aging is associated with notable changes in the endocrine system, and thyroid hormones play a crucial role in these age-related alterations. The functioning of the thyroid gland is closely intertwined with

physical adjustments and various metabolic processes, making it a vital component in the aging process [18]. Although most participants in the KNHANES dataset showed euthyroidism, and overt thyroid diseases were uncommon, our study highlights the significant effect of overt hyperthyroidism as a risk factor for frailty. Excess thyroid hormone levels have been found to be associated with negative cardiovascular outcomes, a factor of importance in the assessment of comorbidities (e.g., hypertension, coronary artery disease, cerebrovascular disease, thyroid cancer, arrhythmia, weight loss, muscle weakness, low PA, and dyslipidemia) [19]. Overt hyperthyroidism is linked with muscle dysfunction and sarcopenia due to its catabolic effects, leading to a reduction in lean muscle mass [20]. Additionally, it contributes to weight loss by increasing the metabolic rate [21], and is associated with an increased risk of osteoporosis [22]. These components are integral to the evaluation of frailty. Furthermore, subclinical hyperthyroidism was associated with a more than twofold higher prevalence of frailty. These findings align with a previous study of 100 veterans 65 years and older enrolled in the Phoenix VA Health Care System [23]. That study demonstrated that subclinical hyperthyroidism was independently associated with frailty, irrespective of FT4 levels. Another study, based on the Osteoporotic Fractures in Men Study, also demonstrated that subclinical hyperthyroidism was associated with a higher prevalence of frailty when compared to euthyroidism [24]. It is plausible that subclinical hyperthyroidism could be associated with similar pathophysiological changes as overt hyperthyroidism, albeit to a lesser extent. While we hypothesized that hypothyroidism would show an association with frailty based on existing knowledge of thyroid dysfunction's potential impact on various health parameters, neither overt hypothyroidism nor subclinical hypothyroidism was a significant factor in our results. In contrast to our findings, a recent study conducted in a population older than 85 years found that subclinical hypothyroidism and TSH levels were associated with frailty diagnosed using the FRAIL scale, which assesses Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight [25]. Subclinical hypothyroidism has been associated with neuromuscular [26], musculoskeletal [27], and cognitive dysfunction [28], which all strongly correlate with frailty. However, we found no significant association. In the elderly, FT4 levels within the low-normal range and higher TSH appear to contribute to healthy aging and improved survival in late life [8]. Lower thyroid hormone levels in this range may result in decreased energy production and requirements, which can prevent catabolism and reduce oxidative stress. This suggests that decreased thyroid function might act as a protec-

tive factor against frailty [29]. Differences in the prevalence of thyroid disease, the age distribution of the participants, and the use of different frailty assessment tools might all have contributed to the disparities between our findings and those of the aforementioned study. Evidence indicates the involvement of the hypothalamic-pituitary-thyroid axis in both aging and frailty. However, it's still unclear if the observed non-causal connection between low TSH and frailty is due to other factors or signifies a causal relationship driven by elevated thyroid hormone levels. Nonetheless, frailty is a modifiable condition. Therefore, exploring the potential risk of frailty associated with thyroid dysfunction, even at a single point, is crucial.

We did not observe a significant correlation between thyroid hormone parameters and frailty. Most of our participants exhibited euthyroid function. In contrast, a study conducted in China reported a positive correlation between TSH and frailty, with an OR of 1.06 (95% CI, 1.0 to 1.11) [28]. Another large Italian cohort study involving individuals over 65 years of age demonstrated that higher TSH levels were associated with increased risk in men, while lower TSH levels were correlated with the risk of frailty in women [30]. It is important to note that these results were analyzed within a normal range of TSH values. Specifically, all participant in our frail group were women. The prevalence of thyroid dysfunction and frailty differ according to sex. Furthermore, it is essential to consider that the confounding factors considered in the previous study differ from those in our study. Additionally, because Korea is an area with iodine sufficiency, we adjusted for UIC as a potential confounding factor in our analysis.

In a subanalysis according to thyroid disease, FT4 was significantly negative correlated with frailty in overt hypothyroidism. Several studies have investigated the effects of levothyroxine replacement therapy on physical performance [31,32], demonstrating its effectiveness in improving outcomes for old patients with overt hypothyroidism [29]. Therefore, considering FT4 levels alongside other clinical indicators can provide a more comprehensive assessment of thyroid status in frail individuals. In contrast to overt hypothyroidism, FT4 and TSH levels in overt hyperthyroidism were associated with a higher OR of frailty. Thyroid hormones have diverse effects on various organs and systems that ultimately affect overall health. For example, thyroid hormone excess is the main risk factor for atrial fibrillation, and the threshold for arrhythmia decreases with age [33]. Musculoskeletal function, which is the core of frailty, becomes a concern in the presence of excess FT4 [34]. Excess thyroid hormone has been linked to various effects, including hemodynam-

ic changes [35], hypercoagulability [36], neurodegeneration [37], and impaired bone health [38]. A study conducted in Rotterdam, that included a sizable population, reported that higher FT4 levels were associated with an increased risk of frailty over time, as assessed using the FI [39]. The age characteristics of the study population in Rotterdam were similar to those in our study. Those findings thus provide additional support for our observations, suggesting that elevated FT4 levels could contribute to the development or progression of frailty. In subclinical hyperthyroidism, high FT4 was correlated with a higher risk of frailty, and high TSH was correlated with a lower risk of frailty. We did not find a consistent correlation between thyroid autoimmunity (based on TPOAb) and frailty. TPOAb was identified as a risk factor for overt hyperthyroidism but not for subclinical hyperthyroidism. This result is consistent with a previous study that investigated the implications of thyroid autoimmunity [40]. In contrast, a population-based study that used the FFP reported finding a low frailty risk in TPOAb-positive women [40]. Our results suggest that the association between TPOAb and the risk of frailty is influenced by thyroid function. Hence, further research is warranted to clarify the precise mechanisms through which TPOAb might influence the onset or persistence of the frailty syndrome.

To the best of our knowledge, this is the first population-based cohort study to comprehensively investigate the relationship between thyroid function and frailty using the well-established FFP tool. Additionally, our study is the largest investigation to date on the association between thyroid function and frailty.

Nonetheless, several limitations of our study should be acknowledged. First, the information on frailty was based on a self-reported questionnaire, which introduces the potential for misclassification. Self-reported measures might not capture the full extent of frailty and can lead to under- or overestimation of its prevalence. Future studies could consider incorporating more objective measures of frailty to enhance the accuracy of assessment. Second, because our study was cross-sectional, we cannot establish a causal relationship between thyroid dysfunction and frailty. We could not track the alterations in thyroid function over time. In our cross-sectional study, we focused on examining the relationship between thyroid dysfunction and frailty at a single point in time. Therefore, longitudinal studies would provide valuable insights into the temporal relationship between them and help to elucidate the complex mechanisms linking thyroid function and frailty. Third, our analysis focused on FT4 and TSH levels without including thyronine (T3). T3 is a biologically active hormone, and its measurement could provide a

more comprehensive understanding of thyroid function in relation to frailty. However, T3 levels were not measured in the KNHANES dataset, so we were unable to examine its association with frailty.

These findings suggest that thyroid dysfunction, specifically overt hyperthyroidism and subclinical hyperthyroidism, could be associated with an increased risk of frailty in older adults. Understanding the relationship between thyroid function and frailty has implications for the management and prevention of frailty and emphasizes the importance of thyroid health in promoting the overall well-being of older populations. Further research is warranted to explore the underlying mechanisms of and potential interventions for this association.

CONFLICTS OF INTEREST

The results do not necessarily reflect the opinion of Medical Excellence Inc., and there is no affiliation.

AUTHOR CONTRIBUTIONS

Conception or design: J.L. Acquisition, analysis, or interpretation of data: Y.J.L., M.H.K., D.J.L., J.M.L., S.A.C., J.L. Drafting the work or revising: Y.J.L., J.L. Final approval of the manuscript: J.L.

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