Thyroid Function and Reduced Kidney Function with Aging in Chinese Older Adults: A Cross- sectional Study

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Abstract

Background: Thyroid function may be a factor influencing renal function in general population. Renal function and thyroid function vary with aging, thus the association of thyroid function and declining kidney function in older adults was different from this in the young and remains controversial. The aim of this study was to estimate association between thyroid function in reference interval and reduced kidney function with aging in Chinese older adults.

Methods: A total of 15729 adults, 23.3% (N= 3624) of which were older population, were collected in the health check-up department of the First Affiliated Hospital of Nanjing Medical University between January 2018 to January 2020.Basic demographic information was collected by physician-administered questionnaire. The variation tendency of thyroid function with aging was investigated by mean of free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulatinghormone (TSH) in subgroups for every 10 years. Associations between kidney and thyroid function were estimated with β value by multiple linear regression and with odds ratio (OR) by multivariable logistic regression models adjusted for age, gender, body mass index and serum urine acid.

Results: In the older population, an increased trend of TSH, a decreased trend of FT3 and little change of FT4 were identified with aging. Estimated glomerular filtration rate (eGFR) remarkably decreased with increasing TSH (β: -0.081) and declining FT3 (β: 0.083) concentrations. Compared with the population in the lowest FT3 quartile (3.10-4.45 pmol/L), the prevalence of eGFR< 75ml/min/1.73m^2 significantly decreased by 22.0% with FT3 4.46-4.81 pmol/L, 27.6% with FT3 4.82-5.20 pmol/L and 34.9% with FT3 5.21-6.8 pmol/L in older individuals (*P* for trend <.001). The OR was 1.315 with high-normal TSH, comparing to low-normal TSH in older persons (*P*: 0.025). Similar results were found between prevalent eGFR< 60ml/min/1.73m^2 and thyroid function. The prevalent reduced kidney function was not remarkably associated with FT4 in the reference range.

Conclusions: This study demonstrated a significant association between thyroid function and kidney function, especially FT3 in older population. The clinician were advised to evaluate renal function with low-normal FT3 and high-normal TSH in case of potential decreased kidney function.

Background

Kidney function declines with aging, which is mainly manifested as a decline in glomerular filtration rate (GFR) and accompanied by decreased tubular function and structural changes [1]. These impairments caused by aging makes the elderly more susceptible to acute kidney injury and increase the propensity to subsequent progressive chronic kidney disease (CKD) [3]. Declining kidney function is accompanied by age-related comorbidities and may be interacted on each other [2, 4].

Thyroid function has been suggested as an influencing factor affecting kidney function through regulation of renal blood flow, renin-angiotensin-aldosterone system, tubular mass and glomerular architecture in the general population [7–9]. Indexes of thyroid function vary with aging, thus the association of thyroid function and declining kidney function in older adults was different from this in the young and remains

controversial [5]. Previous studies demonstrated that thyroid dysfunction was associated with estimated GFR (eGFR) and likelihood of prevalent CKD [6, 17]. No data to date investigate the association between normal thyroid function and reduced kidney function with aging in general Chinese older population.

Therefore, this study was conducted to clarify the association between indexes of thyroid function in reference range and eGFR or the prevalence of reduced kidney function in general older adults, which would provide a new idea for the clinical assessment and intervention of reduced kidney function with aging.

Methods

Participants

This study was a retrospective cross-sectional study. A total of 15653 Chinese adults in the check-up department of the First Affiliated Hospital of Nanjing Medical University were collected in this study between January 2018 to January 2020. All participants underwent standardized physical and neuropsychological examinations. Inclusion criteria were as follows: (1) age ≧ 18 years, (2) BMI: 18.5–28 kg/m^2, (3) indexes of thyroid function in the reference interval, (4) other biological indicators, such as blood glucose (BG), alanine transaminase (ALT), low-density lipoprotein cholesterol (LDL-C) et al, in relative healthy status according to guides based on the Chinese population. Participants were excluded with any of the following conditions: (1) missing serum creatinine (SCr), thyroid hormone values or demographic variables, (2) diffuse echo changes, enlarged thyroid, and absent thyroid by thyroid ultrasound, (3) proteinuria, eGFR < 60ml/min/1.73m^2 in the young or eGFR < 45ml/min/1.73m^2 in the older adults, (4) taking medications affecting thyroid function such as amiodarone, lithium, iodine and antithyroid drugs, (5) history of malignant tumors, kidney disease and other systemic diseases, (6) pregnant status, acute onset or serious other systemic diseases. This study was approved by the ethical review committee at the First Affiliated Hospital of Nanjing medical University (2018-SR-181).

Laboratory Measures

Basic demographic information (age, sex, past medical history, and related medications) was collected by a physician-administered questionnaire. The questionnaire was evaluated for incomplete or inconsistent answers, first by nurses and again by our staff physicians. Body mass index (BMI) was calculated as measured weight (kg) divided by height (m) squared.

Blood samples were collected in the morning after an overnight fast of at least 8 hours. Plasma/serum samples after separation were stored at 4℃ in refrigerated containers and sent to a commercial laboratory (HITACHI,7600, Japan). SCr was measured by an enzymatic method. The above samples were strictly in accordance with the rules of operation, in Olympus AU5400 automatic biochemical instrument (Ft Olympus company). The CLIA immunoassay was used to measure thyroid stimulatinghormone (TSH) (reference range: 0.27–4.2 mIU/L) levels. Free thyroxine (FT4) (reference range: 12–22 pmol/L) and free

triiodothyronine (FT3) (reference range: 3.1–6.8 pmol/L) were measured by microparticle enzyme immunoassays.

Assessment of Kidney Function

Estimated glomerular filtration rate (eGFR) was calculated applying the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. For females, if SCr is ≤ 0.7 mg/dl, eGFR equals to $144\times(Cr/0.7)^{-0.329}\times(0.993)^{age}$, and if SCr is > 0.7mg/dl, eGFR equals to $144\times(Cr/0.7)^{-1.209}\times(0.993)^{age}$. For males, if SCr is ≤ 0.9mg/dl, eGFR equals to $141\times(Cr/0.9)^{-0.411}\times(0.993)^{age}$, and if SCr is > 0.9mg/dl, eGFR equals to $141\times(Cr/0.9)^{-1.209}\times(0.993)^{age}$. eGFR < 75ml/min/1.73m^2 was defined as mildly reduced kidney function. Reduced kidney function was commonly defined as eGFR < 60ml/min/1.73m^2.

Statistical Analysis

Baseline characteristics were shown as means with SDs or numbers with percentages. T-test and Chi-square test were adopted to determine the statistical difference between the young and elderly. We divided total population to seven subgroups according to age and calculated the Means with SD of FT3, FT4 and TSH in each subgroup to investigate the variation tendency of thyroid function with aging. The differences between groups and pairwise comparison were conducted by one-way ANOVA and Duncan's multiple range test respectively. The association between thyroid function and eGFR was assessed by multiple linear regression analysis. We performed multivariable logistic regression analysis to investigate the association between the prevalence of mildly reduced or reduced kidney function and FT3, FT4 or TSH after adjusting for age, gender, BMI, serum urine acid (UA).

Statistical analyses were carried out with IBM® SPSS® statistics version 26.0. (IBM Corporation, New York, USA). Figures were created by Prism 8 (GraphPad, 1992). Two-tailed *P* value of < 0.05 was considered to be statistically significant.

Results

Characteristics of 15653 participants were shown in Table 1. The mean age of total population was 54.36 years, and 23.2% (N = 3624) of which was over 65 years. Compared to the young group, the percentage of female and LDL-C level was significantly lower, when the BMI, SBP, UA, BG were remarkably higher in older persons. The prevalent mildly reduced renal function (defined as eGFR < 75 ml/min/1.73m^2) was 7.5% (N = 1177) in total participants, 2.3% (N = 273) in the young and 24.9% (N = 904) in older adults. The prevalence of eGFR < 60 ml/min/1.73m^2 was 5.5% (N = 200) in older population.

Table 1
Characteristics of the study populations

	Total	Young(< 65ys)	Elderly(≧ 65ys)
N (%)	15653	12029 (76.8%)	3624 (23.2%)
Female (%)	6063 (38.7%)	4921 (40.9%)	1142 (31.5%) *
Age (ys)	54.36 (13.98)	48.66 (10.07)	73.28 (6.43) *
BMI (ml/m^2)	23.62 (2.33)	23.53 (2.35)	23.93 (2.25) *
SBP (mmHg)	128.7 (18.20)	124.48 (16.15)	142.67 (17.64) *
DBP (mmHg)	76.98 (10.84)	76.83 (10.88)	77.5 (10.69)
BUN (mmol/L)	5.13 (1.20)	5.04 (1.15)	5.44 (1.28) *
SCr (mg/dL)	0.80 (0.16)	0.78 (0.15)	0.84 (0.17) *
UA (υmol/L)	338.39 (80.22)	335.5 (80.47)	348.0 (78.64) *
LDL-C (mmol/L)	3.29 (0.8)	3.34 (0.79)	3.11 (0.84) *
BG (mmol/L)	5.55 (1.07)	5.42 (0.95)	6.01 (1.31) *
FT3 (pmol/L)	4.84 (0.56)	4.89 (0.56)	4.66 (0.51) *
FT4 (pmol/L)	17.18 (1.97)	17.21 (1.95)	17.09 (2.05) *
TSH (mIU/L)	2.28 (1.21)	2.23 (1.07)	2.44 (1.59) *
eGFR (ml/min/1.73m^2)	96.79 (14.52)	101.33 (12.12)	81.71 (11.24) *
> 90 ml/min/1.73m^2	11074 (70.7%)	10116 (84.1%)	958 (26.4%)
75–90 ml/min/1.73m^2	3402 (21.7%)	1640 (13.6%)	1762 (48.6%)
60–75 ml/min/1.73m^2	977 (6.2%)	273 (2.3%)	704 (19.4%)
< 60 ml/min/1.73m^2	200 (1.3%)	0	200 (5.5%)

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, BUN: urea nitrogen, SCr: serum creatinine, UA: serum urine acid, LDL-C: low-density lipoprotein cholesterol, FT3: free triiodothyronine, FT4: free thyroxine, TSH: thyroid stimulatinghormone, eGFR: estimated glomerular filtration rate measured by the 2009 CKD-EPI forluma.

* P< 0.05 compared with the young.

Variation Tendency of Kidney Function and Thyroid Function with Aging

The variation tendency of FT3, FT4, TSH and eGFR was shown in Fig. 1. FT3 levels decreased with aging (*P* for trend < .001), and the declining rate was faster in older adults compared with this in the young. We revealed an escalating trend of TSH with aging in subjects over 50 years (*P* for trend < .001). A declining trend of FT4 was revealed with increasing age in subjects younger than 40 years and little change was investigated in population above 40 years. With increasing age, the eGFR level gradually decline.

Association Between Thyroid Function and eGFR

In older individuals, after adjusted for some traditional factors like gender, age, BMI and UA, we validated a positive association between FT3 and eGFR (β = 0.083). This correlation was also revealed in the young (β = 0.094). Besides, the results showed a negative association between FT4 and TSH and eGFR in both groups. It should be noted that TSH and eGFR had much more correlation in the older population (β= -0.081), whereas FT4 and eGFR had much more association in the young (β= -0.056) (Table 2).

Table 2

Association between thyroid function and eGFR [a]

	Young		Elderly	
	β	*P* value	β	*P* value
FT3	0.094	< .001	0.083	< .001
FT4	-0.056	< .001	-0.032	0.032
TSH	-0.046	< .001	-0.081	< .001

eGFR: estimated glomerular filtration rate calculated by the 2009 CKD-EPI formula, FT3: free triiodothyronine, FT4: free thyroxine, TSH: thyroid stimulatinghormone.

[a] Adjusted for some traditional influencing factors like gender, age, body mass index and serum urine acid.

Thyroid Function and Prevalent Reduced Renal Function

The population with GFR < 75ml/min/1.73m^2 were older, more likely to be male and had higher UA. Lower FT3 and FT4 level and significant increased TSH concentrations was investigated in older adults with GFR < 75ml/min/1.73m^2 (Table 3).

Table 3

Characteristics of the population with or without mildly reduced renal function [a]

	Young		Elderly	
Characteristic	eGFR ≧ 75ml/min/1.73m^2	eGFR < 75ml/min/1.73m^2	eGFR ≧ 75ml/min/1.73m^2	eGFR < 75ml/min/1.73m^2
	(N 11756)	(N 273)	(N 2724)	(N 900)
Female (N, %)	4873 (41.5%)	48 (17.6%) *	893 (32.8%)	249 (27.7%) **
Age (years)	48.46 (10.06)	57.31 (6.01) *	72.09 (5.90)	76.9 (6.61) **
BMI (kg/m^2)	23.50 (2.35)	24.61 (1.96) *	23.90 (2.23)	24.02 (2.30)
SCr (mg/dL)	0.78 (0.15)	1.11 (0.11) *	0.78 (0.12)	1.03 (0.15) **
UA (υmol/L)	333.89 (76.70)	404.86 (83.29) *	335.67 (73.82)	385.32 (81.01) **
FT3 (pmol/L)	4.89 (0.56)	4.88 (0.56)	4.70 (0.50)	4.54 (0.52)
FT4 (pmol/L)	17.20 (1.95)	17.27 (1.96)	17.10 (2.04)	17.05 (2.08)
TSH (mIU/L)	2.23 (1.07)	2.37 (0.85)	2.38 (1.42)	2.62 (2.01) **
eGFR (ml/min/1.73m^2)	102.05 (11.28)	70.33 (3.72) *	87.04 (6.07)	65.57 (7.14) **

BMI: body mass index, SCr: serum creatinine, UA: urine acid, FT3: free triiodothyronine, FT4: free thyroxine, TSH: thyroid stimulatinghormone, eGFR: estimated glomerular filtration rate measured by the 2009 CKD-EPI formula.

[a] Mildly reduced renal function defined as eGFR < 75ml/min/1.73m^2.

* P < 0.05 compared with the eGFR ≧ 75ml/min/1.73m^2 group in the young.

** P < 0.05 compared with the eGFR ≧ 75ml/min/1.73m^2 group in older subjects.

After controlling for the effects of age, gender, BMI, and UA, the odds ratio (OR) of prevalent eGFR < 75ml/min/1.73m^2 was 0.994 (95% confidence interval (95%CI): 0.77–1.283) with TSH 1.57–2.13 mIU/L (Prevalent eGFR < 75ml/min/1.73m^2: 229/995), 1.236 (95%CI: 0.967–1.58) with TSH 2.14–2.82 mIU/L (181/824) and 1.315 (95%CI: 1.035–1.67, P: 0.025) with TSH 2.83–4.20 mIU/L (88/513), comparing to TSH 0.27–1.56 mIU/L (402/1292) in the older population (P for trend: 0.038). On the contrary, the prevalence of mildly reduced kidney function significantly decreased by 22.0% (OR: 0.78, 95%CI: 0.631–0.965, P: 0.022) with FT3 4.47–4.81 pmol/L (188/824), 27.6% (OR: 0.724, 95%CI: 0.574–0.915, P: 0.007) with FT3 4.82–5.20 pmol/L (239/939) and 34.9% (OR: 0.651, 95%CI: 0.485–0.875, P: 0.004) with FT3 5.21–6.8 pmol/L (287/1038) compared with the population with FT3 3.10–4.46 pmol/L (186/823) in older persons (P for trend: 0.007). We did not investigate significant correlation between FT4 level in the reference range and the prevalence of eGFR < 75ml/min/1.73m^2 in older people (P for trend: 0.223). In the young group, the

prevalence of eGFR < 75ml/min/1.73m^2 decreased with elevating FT3 levels in reference range (*P* for trend: 0.016), whereas it was not associated with FT4 and TSH concentrations (Fig. 2).

We also analyzed the correlation of prevalent eGFR < 60ml/min/1.73m^2 and thyroid function in the older population. The prevalence of reduced renal function significantly decreased by 41.8% (95%CI: 0.387–0.874, *P*: 0.009) with FT3 4.47–4.81 pmol/L (39/995) and 69.9% (95%CI: 0.14–0.651, *P*: 0.002) with FT3 5.21–6.8 pmol/L (8/513) compared with the population in the lowest FT3 quartile (3.10–4.46 pmol/L) (110/1292) in older persons (*P* for trend: 0.002). Additionally, the prevalence of it increased with elevating FT4 and TSH levels.

Discussion

In older adults, the eGFR levels remarkably decreased with increasing TSH and declining FT3 concentrations. The odds of reduced kidney function were higher with low-normal FT3 and high-normal TSH level. The prevalence of reduced kidney function was not associated with FT4 in the reference range.

We investigated a rapid decrease in FT3 with aging in the older population. This may be due to reduced activity of 5'mono-deiodase, which catalyzes deiodination of T4 into T3, or/and reduced stimulation by TSH with aging [5]. The trend of FT4 concentrations in older population was consistent with previous studies which also demonstrated little change of FT4 concentrations with aging [26]. This stability despite aging may be due to a combination of reduced T4 synthesis and secretion by the thyroid cells and reduced metabolic thyroxine clearance [5]. Increasing in TSH with aging was observed based on this population. The variation tendency of thyroid function and kidney function in this population was consistent with previous studies, thus the subjects in this study are well represented.

The odds of mildly reduced or reduced renal function gradually decline with increasing FT3 concentrations in the reference range. The decreased FT3 level has been proven to be associated with endothelial dysfunction and inflammation, which are pathology of aging and impaired kidney [27]. Some studies showed the prevalence of eGFR < 60ml/min/1.73m^2 was significantly greater in the low T3 condition [13, 22]. Several studies have demonstrated the association between the presence of low T3 condition and acceleration of progression of disease and some adverse outcomes in patients with heart disease or surgery therapy in older adults [13, 22, 25]. Studies and guidelines to date concentrate on the cardio and mental prognosis in patients with low T3 and rare of those pay attention to the kidney prognosis [5, 21]. Thus, our study revealed that low FT3 level even in the reference interval may be a risk factor for the incidence of mildly reduced or reduced kidney function in the older population. Meanwhile, FT3 may be associated with pathology in kidney with aging. Nevertheless, Kidney has an important role in the metabolism and excretion of thyroid hormones, and low serum T3 is a common thyroid hormone disturbance during illness including impaired kidney function [21, 27].

The significant association was investigated between TSH and eGFR or reduced kidney function in older people. The prospective Kangbuk Samsung Health Study has shown that high-normal levels of TSH had an increased risk of prevalent reduced kidney function [12]. Besides, A study from the Netherlands showed

similar result in older population (age ≧ 85years)[10]. Conversely, some studies based on the general population demonstrated that TSH was not associated with risk of incident reduced kidney function [17, 20, 24]. The differences in race, age and included correction factors may result in these conflicting results. Therefore, as an important diagnostic and efficacy evaluation index in current clinical practice, the association of TSH and reduced kidney function needs to be further investigated to figure out whether TSH was an appropriate indicator and follow-up observation index in the elderly with reduced kidney function.

FT4 levels level off in population 65 years and older. Significant association between FT4 and prevalent reduced kidney function was not investigated in older adults. This result was consistent with previous studies [12, 15]. Meanwhile, some studies demonstrated inconsistent results about the positive or negative correlation of FT4 and kidney function [10, 11].

There was not significant association between normal FT4, TSH and prevalence of mildly reduced kidney function in the young, which was different from these in the older population. Therefore, the reference interval for general population may be not suitable for older adults.

Thyroid function could influence kidney function through several mechanism according to previous studies. Elevated thyroid function may improve kidney function through regulation of renal blood flow, renin-angiotensin-aldosterone system, nitric oxide synthase activity and sodium reabsorption [8]. This mechanism may account for the positive relationship between FT3 and kidney function and negative association between TSH and renal function in this study. However, some studies recently verified that elevated thyroid hormone levels can enhance oxygen consumption and production of reactive oxygen species (ROS), which may subsequently induce DNA damage and cell apoptosis [30, 31]. Oxidative stress, which is caused by the increased production of ROS, is a pivotal factor in reduction of renal function, through glomerular damage, renal ischemia, inflammation, solute and water reabsorption and endothelial dysfunction [28, 29]. It has also been suggested that a low thyroid function in the elderly represents a physiological downregulation of the hypothalamic-pituitary axis, possibly benefitting life expectancy [16, 18]. In addition, a possible explanation lies in a slower metabolic rate which related to an increased survival [14]. The mechanism is complex between thyroid and kidney function, so further studies are needed to figure this out and may provide a new perspective on the development of aging related reduced kidney function.

The data presented here could be promising for clinical applications in older adults. The evaluation of thyroid function is needed in older patients with pathological decline in kidney function. Meanwhile, when thyroid function disorder is diagnosed, even low FT3 or high TSH level in the reference range, the clinician should access the patient's kidney function at the initial visit and during the follow-up in case of potential decreased kidney function. Furthermore, FT3 may be a better index to evaluate the clinical curative effect of patients with thyroid function disorder and renal insufficiency according to the association between FT3, FT4 and TSH and prevalence of mildly reduced or reduced kidney function. Additionally, considering the change of thyroid function with aging and prognosis of related organs, the conference intervals of thyroid hormones in the elderly need to be further discussed.

Our study is based on a large check-up population within a real-world clinical environment discussing the association between thyroid and kidney function in the Chinese older adults and observing the difference

compared to the young. In addition, we performed adjustments for some identified and potential confounders. UA, as an identified risk factors for decreasing in renal function, was not included in the calibration in previous studies. Most importantly, we firstly analyzed association in detail between normal FT3 levels and kidney function in the Chinese older population.

Our study has several limitations that may influence our conclusion. First, we used CKD-EPI formula based on SCr to estimate GFR other than golden standard. EGFR may not be a good approximation of kidney function in this association as thyroid function could possibly influence SCr levels via muscle metabolism and volume status [23], but our prior research investigated the high accuracy of CKD-EPI formula in the Chinese older adults. We also observed the correlation between thyroid function and eGFR by FAS formula which perform well in the healthy older people, and obtained similar result. In addition, a study demonstrated that the incidence of thyroid disease was significantly elevated in the population with decreasing in kidney function [19]. It is unclear whether thyroid hormone alterations are the cause or consequence of reduced kidney function. Further studies are required to elucidate the causal relationship between thyroid and kidney function.

Conclusions

In conclusion, we demonstrated a significant association between thyroid function and kidney function, especially FT3 concentrations in older adults. Further studies need be detected to investigate the influence and mechanism of thyroid function on kidney function in the older population, and to detect an adaptive method and timing of interventions and reference range for older individuals with thyroid diseases to get a better kidney prognosis.

Abbreviations

eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; SCr: serum creatinine; TSH: thyroid stimulatinghormone; FT4: Free thyroxine, FT3: free triiodothyronine; BMI: body mass index; BUN: urea nitrogen; UA: serum urine acid; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; BG: blood glucose; ALT: alanine transaminase; LDL-C: low-density lipoprotein cholesterol.

Declarations

Ethics approval and consent to participate

This study was approved by the ethical review committee at the First Affiliated Hospital of Nanjing medical University (2018-SR-181).

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conception and design, acquisition of data, analysis and interpretation of data, drafting and revising the article, and final approval of the version to be published: WL, BY and ZY. Revising the article for important intellectual content and final approval of the version to be published: YZZ and ZB. Acquisition of data and final approval of the version to be published: ZQ. Conception and design, acquisition of data, analysis and interpretation of data, revising the article for important intellectual content, and final approval of the version to be published: ZWH.

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Figures

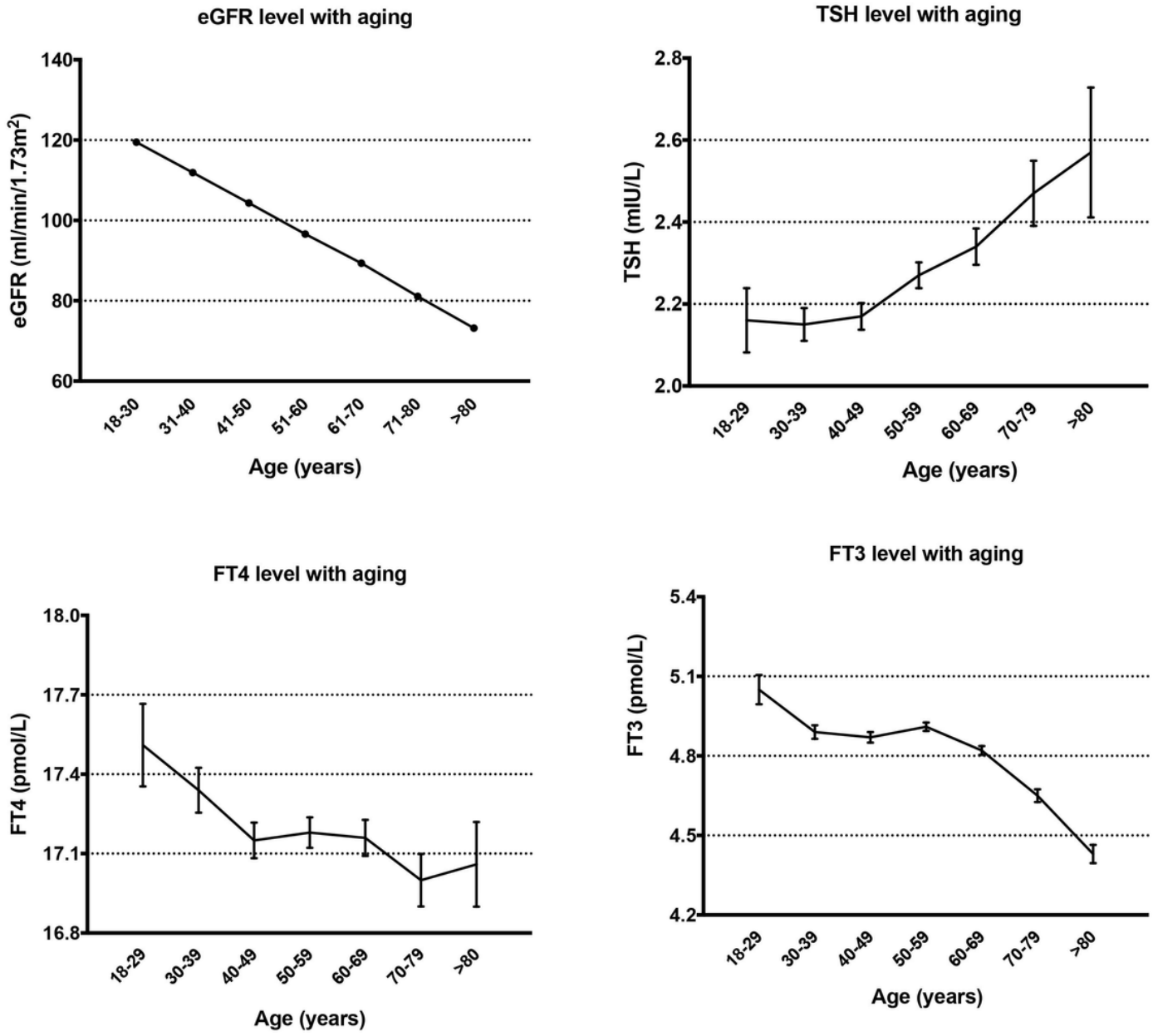

Figure 1

Variety tendency of indicators of thyroid function and eGFR FT3: free triiodothyronine, FT4: free thyroxine, TSH: thyroid stimulatinghormone, eGFR: estimated glomerular filtration rate by CKD-EPI formula.

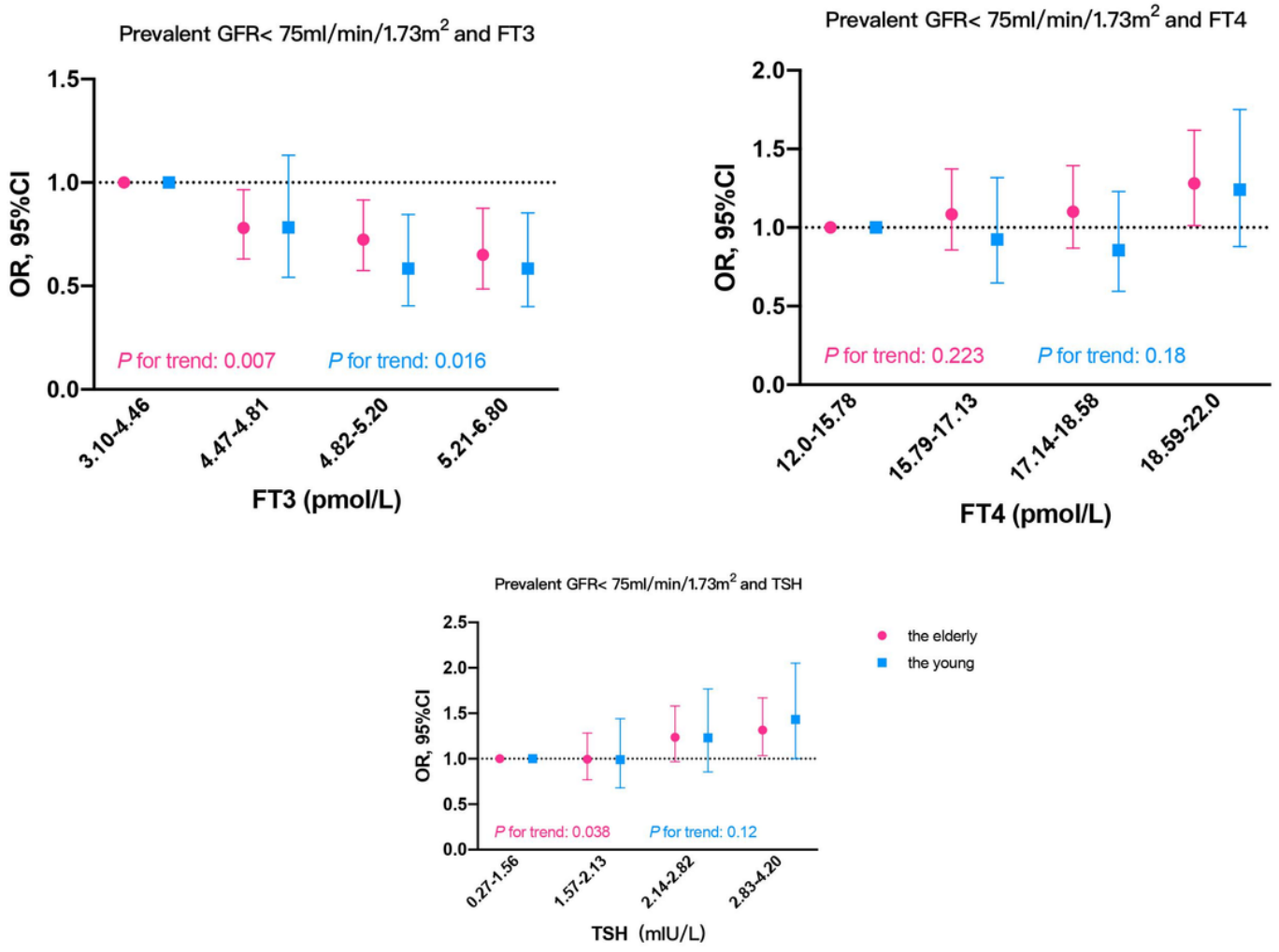

Figure 2

Association between FT3, FT4 and TSH and prevalent GFR < 75ml/min/1.73m2 FT3: free triiodothyronine, FT4: free thyroxine, TSH: thyroid stimulatinghormone, OR: odds ratio, 95%CI: 95% confidence interval.